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DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

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Functional Tests of the Liver; A Clinical Review*

By George B. Eusterman, M.D., *Division of Medicine, Mayo Clinic, Rochester, Minnesota*

PROGRESS in our knowledge of the function and diseases of the liver has unfortunately been slow. With few exceptions it is only in recent years that intensive, coördinated effort on the part of the clinician, surgeon and research worker has begun to yield results of practical value. At long intervals in the past important contributions have been made by the anatomist, pathologist and physiologist, laying the foundation for some of our present conceptions and advances, but the sum total of indubitable facts has not been sufficient to make their application to the solution of our daily problems practicable. Cirrhotic changes, the result of a tuberculous, carcinomatous, syphilitic or extrahepathic obstructive process, are fairly well understood, but the classification of the other types of cirrhosis is still unsatisfactory.[12] In our ignorance as to their causes such classification is based on anatomic changes and functional disturbances which may be variously interpreted.[11] While we have always realized that the liver, like the spleen, suffers in silence, and that the former has unusual reserve and regenerative power, and is an organ of various metabolic, defensive and excretory functions (some of which until recently were not clearly understood), of its functional derangements we have been in the main blissfully ignorant.

Those who have had an opportunity to observe closely many cases, and have given much thought to the subject are impressed with our limitation in this field, and particularly with our inability always to differentiate the various types of jaundice and cirrhosis. Except perhaps in the field of pancreatic disease, exact knowledge bearing on etiology, diagnosis and prognosis leaves more to be desired than in most other departments of clinical medicine. Therefore, any procedure which gives promise of shedding light where there has been so much darkness should claim our sustained interest and encouragement.

In the last fifteen years investigations in various problems of research awakened scientific enthusiasm with regard to the biliary system. Chief among these are the results of physiologic research in which such investigators as Whipple, Blankenhorn, Rous, McMaster, Mann and his co-workers and Aschoff stand out; for example: investigations in the problems of dis-

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sociated jaundice, especially those of the French school; studies concerning several recently recognized clinical varieties of jaundice; the formulation of a practical clinical classification of jaundice; Aschoff's contribution relative to the structure and important functions of the reticulo-endothelial system; extensive research directed to the function of the gallbladder; the elucidation of the pathogenesis of cholecystitis, hepatitis and biliary calculus; inquiries into the formation of urobilin and urobilinogen; the identification, chemical composition, and metabolism of the chief biliary constituents, bile pigment, cholesterol and the salts of bile acids; surgical advances in the treatment of certain diseases of the hematopoietic system in which the liver often participates; analysis of complications occurring in surgical lesions of the gallbladder and ducts which often implicate the liver, and in postoperative sequelae such as hepatic insufficiency,[22] and evolvement of biochemical methods to detect functional changes in disease of different organs, which resulted in the discovery of such familiar procedures as the van den Bergh test for serum bilirubin, the icterus index, and the Rosenthal test;[17] the latter had its origin in the researches of Rowntree, Horwitz and Bloomfield.[17]

It may be appropriate to call attention again to the fact that advances in medical science are often dependent on purely technical methods; the contrast-meal, the electrocardiogram and the cholecystogram are modern examples. While too much may have been claimed for the Lyon method of transduodenal biliary drainage from a diagnostic and therapeutic standpoint, nevertheless this procedure has done as much or more to turn a flood of attention to the investigation of problems referable to the biliary tract than anything else. In this respect alone the method has served a useful and timely purpose and has therefore amply justified its existence.

THE MORE IMPORTANT FUNCTIONAL TESTS OF THE LIVER

Difficulties peculiar to the liver, with respect to study of its function, unlike those of the kidney, have been repeatedly emphasized in literature. Owing to various physiologic activities, a large number of tests have been devised as clinical indexes to functional changes in the organ. Many of them have already been discarded as of little, if any, value. Based on a combined clinical, experimental and pathologic study, the following have been found of major importance:

1. *The van den Bergh test (direct and indirect reaction).*—This test determines the nature and amount of bile pigment in the serum. While the icterus index method is simpler, and preferred in many instances on that account, the van den Bergh test has the following advantages: (a) it distinguishes jaundice due to complete obstruction from hemolytic icterus; (b) it shows no deviation from the normal in cases of carotinemia, and (c) it lessens personal error in the reading, since one is less influenced by the variations in the color of the serum. The test is of primary importance in jaundiced patients, and is of greatest practical application in cases of obstructive jaundice. Moreover, it

furnishes a quantitative index for the degree of jaundice observed in the various toxic or infectious states, and it demonstrates the presence of latent icterus.

2. *The phenoltetrachlorphthalein or bromsulphthalein test of Rosenthal*—This test has its greatest clinical value in cases of hepatic disease in which jaundice is not present; portal cirrhosis is a good example. In cases of jaundice the results parallel the bilirubin estimations, for icterus dominates the clinical picture and laboratory data. The dye test, in all probability, is only a measure of excretory function; a negative test, like a negative Wassermann test, does not exclude disease. Diffuse involvement is more likely to cause retention of the dye than a circumscribed lesion, and the amount of dye retained is not necessarily indicative of the degree of involvement. The test is not prognostic in a strict sense. The great reserve and regenerative capacity of the organ, together with the fact that disturbance of one function does not necessarily affect other functions, and the non-existence of any single test that is a measure of all the functions of the liver, are some of the reasons which delimit the value of all present functional tests.

3. *Bile salts in the blood and urine.*—Certain investigators regard the other two constituents of the bile, cholesterin and bile salts (cholates) of greater clinical importance than the pigment. The former is considered the major factor in the formation of biliary calculi, while the latter is believed to be the cause of such toxic manifestations as pruritus, mental depression and bradycardia. The problem with regard to the bile salts, however, is not yet solved. A modified and standardized Pettenkofer test developed in the laboratories of the Mayo Clinic, although still imperfect, serves to indicate adequately relative changes in the bile salts of the blood.

Other tests, the nature and significance of which are more familiar, include determination of the coagulation time of the blood, fragility of the erythrocytes, and the amount and character of the bile and its products in the urine, stools and duodenal contents. Certain investigators in this field have ascribed to other procedures, especially to the estimation of urobilinogen in the freshly voided urine, a peculiar value.[16-20-21] Others again regard all functional tests as of limited value. But daily contact with cases of hepatic disease, and group investigations of the problems presented, convince us that the various tests with which we have familiarized ourselves, especially the dye and van den Bergh tests, are of considerable importance in diagnosis and treatment. They have at least served to stimulate a healthy interest in problems concerned with diseases of the liver and have made us realize our shortcomings in this field.

Results of Functional Tests in Various Diseases of the Liver

Several thousand van den Bergh and Rowntree-Rosenthal tests have been carefully carried out according to the technic described by Greene, Snell and Walters. Table 1 shows parallelism in the results of quantitative serum bilirubin estimations and

dye retention in cases of jaundice. It is only in those cases of disease of the liver or impairment of function without jaundice, that the dye test may be of value, such as portal cirrhosis, dissociation jaundice, metastasis to the liver, toxemia of pregnancy and hematemesis or melena provoked by latent or advanced cirrhosis of the liver.[5] In significance if it shows increased values. In cases of cholecystic disease and jaundice, with 4 or 5 mg. of serum bilirubin, there is retention of dye. In such cases, cholecystography is of limited value, for the dye used in this test is closely related, chemically, to the dyes, ordinarily used for the test of hepatic function,

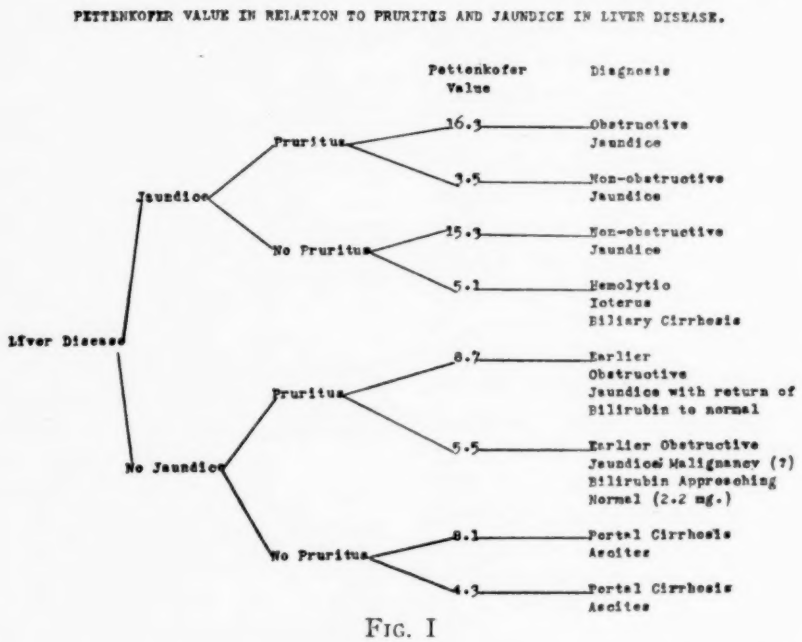

FIG. I

calculous or noncalculous cholecystitis both tests almost uniformly show normal values in the absence of jaundice. The associated hepatitis is undoubtedly too circumscribed to provoke functional changes. Therefore, the observations in the Mayo Clinic are not in accord with those of Laird, Brugh and Wilkerson, who would ascribe definite diagnostic value to functional studies in this condition. Of course the estimation of serum bilirubin following obscure abdominal colic may occasionally be of diagnostic and therefore may be retained by the liver.

In the discussion of cirrhosis of the liver, two main groups are considered: (1) portal cirrhosis, with its clinical variations as regards size of the liver, presence or absence of ascites, and jaundice; the latter is seen only in the terminal stage of the disease, and (2) biliary cirrhosis as the result of extrahepatic obstruction, and its absence; unlike the first group, jaundice is clinically the chief symptom, the liver is enlarged, and ascites is rare and

usually terminal. The spleen may be enlarged in either group. As stated, the dye test is of particular value in the diagnosis and study of cases of portal cirrhosis in which it is apparently an index to the existing functional balance between degenerative and reparative changes in the liver, which condition is largely independent of the amount of ascitic fluid present. While jaundice is not a striking manifestation in portal cirrhosis, estimations of serum bilirubin showed the presence of latent icterus in several cases. In all types of biliary cirrhosis such estimations have been particularly useful in ascertaining the degree of bile retention, which is uniformly present but is more marked than would usually be expected from the degree of bilirubinemia. This proportion is perhaps evidence of the pathologic changes in the liver. In the terminal stages of cirrhosis, irrespective of whether it is primarily portal or biliary, the clinical picture and pathologic and functional changes may be indistinguishable. Diagnostic differentiation, then, is mainly dependent on the history of the case, which includes in chronologic sequence all the details of remote events.

A clinical study embodying functional tests has been made in five cases of apparent dissociation jaundice by McVicar and Weir. This is a condition characterized by the presence of persistent pruritus, heretofore considered as due to an appreciable retention of bile salts without associated icterus, or without enough retention of pigment to be discernible in the skin or sclerotics. In several of these cases the symptoms and signs (icterus and enlarged liver and spleen) were characteristic of biliary cirrhosis. The van den Bergh reaction in all cases was direct. The serum bilirubin in three of the cases was normal in amount, although abnormal qualitatively. In all the cases the dye retention was marked. Attention was called to the fact that in all unexplainable cases of generalized pruritus, hepatic function should be investigated. In some instances, 2 grains of calomel given daily in divided doses, two or three times a week, for a variable period, is effective in relieving pruritus. It was not conclusively shown that the pruritus was due to the presence of an increased amount of bile salts in the tissues. Rowntree, Greene and Aldrich have recently reported their results of quantitative Pettenkofer values in the blood based on several hundred determinations that have been carried out in the wards. The Pettenkofer value of normal blood varies from 2.5 to 6 mg. (in terms of glycocholic acid) for each 100 c. c. Increased Pettenkofer values are frequently encountered clinically in hepatic disease. High values are most common in the presence of jaundice and in the earlier rather than the later stages of obstructive jaundice. High values may be found in cirrhosis of the liver in the absence of jaundice. Pruritus is commonly encountered in jaundice and is frequently associated with high Pettenkofer values. However, a direct causal relationship is lacking, since high values may persist over periods of weeks without pruritus, and itching in chronic disease of the liver may be marked when the Pettenkofer value is strictly normal.

With high Pettenkofer values, tachycardia or normal pulse rate is encountered more frequently than is bradycardia. The level of the Pettenkofer values does not seem to bear a direct causal relationship to decreased coagulability of the blood or to hemorrhage in cases of jaundice. Further clinical and experimental studies relating to the amount of bile acids in the blood and tissues, and the effects of their altered concentration on various physiologic functions, are in progress (Table 1).

My experience with tests of hepatic function in toxemia of pregnancy has been limited. Certain authorities believe that the pregnant state taxes hepatic function to the utmost.[29] Benda maintains that during the second half of pregnancy, and especially during labor, the reticulo-endothelial system is functionally impaired. King, Naujoks, and others, have reported their experiences with the van den Bergh and dye tests in this condition.

Functional changes in the liver are apparently not extensive enough to be of clinical significance in most diseases of the hematopoietic system (hemolytic jaundice, pernicious anemia, polycythemia, leukemia, and splenomegaly of the Gaucher type.[8] An increase in serum bilirubin is of value in the differential diagnosis of hemolytic anemia and the ordinary secondary types of anemia. The serum bilirubin is also an index in following the course of a hemolytic crisis after transfusion. The dye test may show changes in cases of splenic anemia, giving a clue to the severity of the cirrhotic process in the liver. The test would, then, seem to be of some diagnostic and prognostic value. (Table 2.)

CERTAIN CLINICAL ASPECTS OF JAUNDICE

Since jaundice is the most striking single tangible sign of hepatic disease or dysfunction, a brief review of its salient features may not be amiss. McNee has classified jaundice into three main types, all of which have practical application. It is apparent that certain clinical types must be placed in two of the classifications; for example, cases of hemolytic jaundice with stone in the common duct, cases in which toxic changes in the hepatic cells or varying degrees of biliary cirrhosis are combined with definite obstruction of the extrahepatic bile ducts, whether due to stone or benign stricture. Leaving out of consideration those varieties of jaundice met with as a consequence of many acute infectious and protozoal diseases, or as the result of some definite toxic agent, there remains that large familiar group observed in daily practice that so frequently gives rise to difficulties in diagnosis. The majority of such cases, from a practical diagnostic and therapeutic standpoint, might be conveniently grouped into surgical, and nonsurgical types. In the former, as a rule, pain is an outstanding feature, the clinical course is usually characterized by recurrent attacks of pain, vomiting, and so forth, and the familiar associated symptoms are invariably coincident with the painful phenomena. The onset of carcinoma of the head of the pancreas is frequently painless and insidious, such as is seen in toxic or infectious types of jaundice. It must be remembered,

however, that this disease is not infrequently present in the absence of jaundice, especially in the earlier stages of the disease, and pain may be an early and predominant symptom, although usually it differs in character and degree from that of a stone in the common duct.[4] On the other hand, stone in the common duct may or may not be associated with the familiar colic, clay-colored stools, chills and rigor. The characteristic clinical symptoms and signs of both stone in the common duct and carcinoma of the head of the pancreas, as well as other entities, may frequently be atypical enough so that a differential diagnosis can only be made by careful study and observation of the patient in hospital, all available methods of diagnosis being applied at the same time. I believe that icterus as the result of disease confined to the gallbladder itself is usually transient, usually lasting about three or four days. Persistent jaundice complicating cholecystic disease is chiefly the result of an inflammatory, infectious or malignant process, usually affecting the extrahepatic ducts and, less frequently, the liver or pancreas. After operation on the biliary tract, the possibility of benign stricture as a cause of recurrent jaundice must always be considered. It is estimated that about one-third of the patients with such strictures give a history of typical biliary colic. In this connection emphasis must be placed on the injury to the vascular and biliary tree by long-standing obstruction of the common duct, which has been so well brought out by the studies of Counseller and McIndoe. The severity of this injury is not sufficiently appreciated by either the physician or the surgeon. The results of obstruction are most marked and rapid in cases of carcinoma of the head of the pancreas. In such conditions the serum bilirubin may be as high as 25 to 30 mg. for each 100 c. c. Low-grade, long-standing icterus in a youth or adult, without pruritus, with moderate enlargement of the spleen, and bile in the stool but none in the urine all suggest the diagnosis of hemolytic icterus. In cases of recurring or protracted jaundice, associated with pruritus and pain, stone in the common duct, cholangeitis, carcinoma of the head of the pancreas, chronic pancreatitis, and benign stricture should be considered as possibilities in the order mentioned: Carcinoma of the gallbladder, ducts, or papilla, and primary carcinoma of the liver are comparatively rare. It must be remembered that the commonest lesion in the liver is metastatic carcinoma which may have its origin in carcinoma of any organ situated in the peripheral portal system. In rare instances the metastasis to the liver is more in evidence than the original growth.

The nonsurgical or medical types of jaundice are largely of a toxic or infectious nature, intrahepatic in origin, and invariably painless. They may be associated with an enlarged, tender liver. Pruritus preceding painless jaundice by weeks or months is important diagnostically, as it suggests that the lesion producing the icterus is intrahepatic. Hemolytic forms of jaundice, whether of the acquired or congenital type, are also painless as a rule. It must be remembered, however, that in 58 per cent of such cases disease of the gallbladder is associated,

including pigment stones in the extrahepatic ducts, in which event complicating factors are introduced.[6] In experienced hands, intrahepatic forms of jaundice can often be differentiated from obstructive types, and this obviates needless operations. Data derived from an examination of the bile, and estimation of pancreatic ferments obtained by single or repeated transduodenal biliary drainage are of diagnostic importance in this respect when taken in conjunction with other clinical evidence.

Jaundice that follows late after arsphenamine treatment must always be borne in mind.

In the physical examination special attention is paid to the size, consistency and form of the liver; palpability of the gallbladder; rigidity and tenderness over the right rectus; the presence of compensatory venous circulation on abdomen or back; the character, distribution and degree of jaundice, if present; determination of the presence or absence of ascites, metastasis, and purpuric areas; evidence of pruritus, and the gross appearance of the feces and urine.

In the last analysis a proper differential diagnosis depends mainly on time-honored clinical methods, including a complete history, with the appearance of the symptoms in chronologic order, and emphasis on the more important episodes, and a systematic physical examination, in addition to the routine examination of the urine and blood, including the determination of coagulation time, and fragility tests.

TREATMENT OF DISEASES OF THE LIVER

A wider understanding of the liver and its diseases should result in more effective treatment. It should affect the principle of medical management, increase one's ability to determine the degree of surgical risk and improve surgical judgment and surgical results. Encouraging progress has been made, especially in the preoperative preparation of the jaundiced patient, in removing and controlling ascites of portal cirrhosis and in the treatment of the toxemias associated with hepatic insufficiency. A condensed but inclusive outline prepared by Rowntree, is as follows:

Prevention.—Care of acute infections and chronic foci, especially intra-abdominal foci; care relative to the use of alcohol, condiments, chloroform, arsenic, phosphorus, copper, phenylhydrazin, and tar, and care in industry with phosphorus, "aëroplane dope", and picric acid.

Treatment.—Constitutional specifics: arsphenamine, iodide, mercury, emetin, quinine, and vermicides. Hepatic specifics: water, glucose, and calcium.

Functional restoration.— Relief of biliary obstruction: transduodenal biliary drainage. Relief of portal obstruction: Talma-Morrison operation, splenectomy, paracentesis, the administration of merbaphen, and ammonium salts, and restriction of salt and water. Hemolysis: splenectomy. Congestion: digitalis, diuretics, and restriction of salt and water. Protection from hemorrhage in jaundice: calcium chloride, transfusion, carbohydrates and water. Symptomatic relief of pruritus: calomel, emetin, diathermy, and sweating. Relief of gastro-intestinal disturbances: diet and sedatives.

TABLE 1

Illustrative cases

DISEASE	Phenoltetrachlorphthalein retention after one hour, per cent	Serum bilirubin, mg.
	3.0*	1.0*
Obstructive jaundice	30.0	25.0
Carcinoma of head of pancreas with obstruction	36.0	35.7
Metastatic carcinoma of liver with icterus	28.0	36.2
Infectious jaundice	25.0	17.3
Toxic jaundice and pneumonia	15.0	8.7
Syphilitic hepatitis with jaundice	26.0	13.1
Myocardial insufficiency and jaundice	30.0	12.7
Toxic jaundice with exophthalmic goiter	22.0	20.4
Metastatic carcinoma of liver	22.0	2.4
Biliary cirrhosis	17.0	2.6
Atrophic cirrhosis	8.0	1.0
Toxemia of pregnancy	8.0	0.5
Carcinoma of stomach without metastasis	2.0	1.0
Chronic cholecystitis	2.0	1.4

*Normal person.

TABLE 2

Results of functional tests in various diseases of the liver

	Cases	BILIRUBIN			BROM-SULPHALEIN			BILE ACIDS		
		Minimum, mg.	Maximum, per cent	Positive	Minimum, mg.	Maximum, per cent	Positive	Minimum, mg.	Maximum, per cent	Positive
Normals										
Laboratory workers	40	0.2	1.0	0	0	2	0	2.6	5.1	0
Hospital patients	70	0.2	1.8	0	0	10	0	2.6	5.2	0
Chronic cholecystitis	40	0.2	1.9	0	0	30	8	3.0	5.7	0
Obstructive jaundice										
Common duct stone	14	2.4	12.8	14	20	60	14	3.4	8.8	6
Stricture of duct	15	1.2	9.1	9	10	60	15	3.7	10.4	2
Tumor of pancreas	8	10.2	33.4	8	14	96	8	3.0	19.8	5
Carcinoma										
No hepatic involvment	14	0.2	0.9	0	1	12	2	3.0	3.8	0
Metastasis, no jaundice	36	0.2	5.8	2	2	72	31	2.0	8.0	6
Metastasis and jaundice	6	3.0	39.6	6	40	64	6	4.1	16.5	3
Hemolytic jaundice	16	2.9	8.7		0	8		3.1	6.2	1
Pernicious anemia	8	0.8	4.6		0	8		5.3	6.2	1
Splenic anemia	20	0.2	2.8	2	0	60	15	3.4	6.2	1
Myocardial failure with passive congestion	30	0.2	4.5	2	8	64	25	2.7	5.4	0
Hypertension	16	0.2	1.7	0	0	8	0	3.2	5.7	0
Portal cirrhosis										
Small liver	16	0.6	2.2	3	6	60	14	3.9	8.1	2
Large liver	20	0.6	3.1	7	5	64	18	3.8	7.2	3
Biliary cirrhosis										
Obstructive type	11	1.2	7.3	7	20	44	11	2.7	14.3	4
Nonobstructive type	9	1.6	17.8	7	24	56	9	5.0	8.0	3

BIBLIOGRAPHY

(1) Aschoff, Ludwig: Lectures on Pathology. New York, Paul B. Hoeber, 1924, 365 pp.

(2) Benda, Robert: Das Reticulo-endotheliale System in der Schwangerschaft: Eine experimentell-klinische Studie. Berlin, Urban and Schwarzenberg, 1927, 75 pp.

(3) Counseller, V. S. and McIndoe, A. H.: Dilatation of the bile ducts (hydrohepatosis). Surg., Gynec., and Obst., 1926, xliii, 729-740.

(4) Eusterman, G. B.: Carcinoma of the pancreas: a clinical study of 138 cases. Tr. Am. Gastro-enterol. Assn., 1922, 126-137.

(5) Eusterman, G. B.: Unfamiliar aspects of hematemesis and melena. Med. Clin. N. Amer., 1926, x, 485-498.

(6) Giffin, H. Z.: Hemolytic jaundice: a review of seventeen cases. Surg., Gynec., and Obst., 1917, xxv, 152-161.

(7) Greene, C. H. Snell, A. M., and Walters, Woltman: Diseases of the liver. I. A survey of tests for hepatic function. Arch. Int. Med., 1925, xxxvi, 248-272.

(8) Greene, C. H. and Conner, H. M.: Diseases of the liver. V. A comparative study of tests for hepatic function in certain diseases of the hematopoietic system. Arch. Int. Med., 1926, xxxviii, 167-185.

(9) King, E. L.: Liver function tests in the toxemias of pregnancy. Am. Jour. Obst., 1926, xii, 577-585.

(10) Laird, W. R. Brugh, B. F., and Wilkerson, W. V.: Liver function studies and their clinical correlations. Ann. Surg., 1926, lxxxiv, 703-713.

(11) MacCallum, W. G.: A text-book of pathology. Philadelphia, W. B. Saunders Company, Ed. 3, 1924, p. 319.

(12) Mayo, W. J.: The liver and its cirrhoses. Jour. Am. Med. Assn., 1918, lxx, 1361-1364.

(13) McNee, J. W.: Discussion on jaundice. Brit. Med. Jour., 1924, ii, 495-498.

(14) McVicar, C. S., and Weir, J. F.: Dissociated jaundice. Med. Clin. N. Amer., 1926, x, 499-508.

(15) Naujoks, H.: Leberfunktionsprüfung mit Tetrachlorphenolphthalein bei Schwangerschaftstoxikosen. Zentralbl. f. Gynäk., 1925, xlix, 2755-2758.

(16) Ray, H. M.: Present status of liver function tests. Ann. Clin. Med., 1926-1927, v, 176-184.

(17) Rowntree, L. G.: Some contributions to our knowledge of diseases of kidney and liver. Part II. Can. Med. Assn. Jour., 1926, xvi, 1437-1442.

(18) Rowntree, L. G., Greene, C. H., and Aldrich, Martha: Quantitative Pettenkofer values in blood with special reference to hepatic disease, a preliminary report. Jour. Clin. Invest. (In press.)

(19) Rowntree, L. G., Hurwitz, S. H., and Bloomfield, A. L.: An experimental and clinical study of the value of phenoltetrachlorphthalein as a test for hepatic function. Bull. Johns Hopkins Hosp., 1913, xxiv, 327-342.

(20) Schneider, J. P.: The clinical application of the newer knowledge of the biliary function. Minnesota Med., 1926, ix, 631-645.

(21) Wallace, G. B., and Diamond, J. S.: Significance of urobilinogen in the urine as a test for liver function, with a description of a simple quantitative method for its estimation. Arch. Int. Med., 1925, xxxv, 698-725.

(22) Walters, Woltman, and Mayo, W. J.: Abnormal function of the liver. Jour. Am. Med. Assn., 1925, lxxxv, 883-886.

Results of Liver Function Tests*

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DURING the past three years much has been said and written about liver function tests. While everyone who has worked with the various tests feels that these laboratory examinations add some information to the understanding of liver disturbances, as yet no final statement has been made as to their value in the observation and diagnosis of diseases of the liver. The correlation of laboratory findings and the clinical picture presented by the individual case has been difficult, and we feel that it is only by extensive observations that such correlations will be obtained. In order to gain first-hand information in our own cases, as well as to add to the data being accumulated on this subject, somewhat less than a year ago we began to carry out the several liver function tests in cases in which an impairment of the liver was either obviously present or was suspected. The purpose of this paper is to report the results of some of these studies.

We have used the bromsulphthalein dye test; the levulose tolerance test; and both the van den Bergh and the icterus index tests in the estimation of the serum bilirubin. The Widal hemoclastic crisis test was not used because the time and the technique necessary for securing accurate data make it unsuitable for clinic study. In the hands of some observers, however, the Widal reaction test has proved to be of distinct value, and perhaps in the future we shall find it necessary to add this test to our study of disease of the liver.

The levulose tolerance test has proved to be of little value in the early stages of liver disease, and even in late stages it gives very slight evidence of the lowering of tolerance. It is probable that in the function of conversion of fructose to glucose the liver has an extremely large factor of safety. Most of our data, therefore, have been acquired by the use of the bromsulphthalein dye test and by the estimation of serum bilirubin. Bromsulphalein is the only dye we have used during the past ten months. Some few years ago phenoltetrachlorphthalein was tried, but early in our experience we met with an unfortunate accident—thrombosis of the femoral vein following the intravenous administration of the dye in the arm. The dye tests were discontinued at that time until Rosenthal brought out the newer dye, bromsulphthalein. This dye is a distinct improvement over former reagents, as it fulfills almost all the

*Clinical discussion given before the American College of Physicians at the Cleveland Clinic, February 22-25, 1927.

requirements for a perfect testing agent. First, it is nontoxic even in rather large doses—we have never seen evidence of thrombosis and we have used it in over 80 cases. Second, it is taken up entirely by the liver, practically none being excreted by the kidneys. In this respect also it is better than phenoltetrachlorphthalein. Third, the time required for the test is short, thirty-five to forty minutes being sufficient, a feature which is obviously important in dealing with nonhospitalized cases. We feel, therefore, that bromsulphthalein is distinctly the reagent of choice in dye tests for liver function.

It is not necessary to give the details of the technique of this test; the procedure is quite simple and is well described in Rosenthal's original article. I wish merely to emphasize its value in the observation and diagnosis of liver disturbances.

As I said before, we have made 80 examinations in 63 individuals. Among these 63 cases, 31 showed retention of dye, the degree of retention ranging from five to 70 per cent. In order to correlate these findings with the clinical diagnoses it seems expedient to separate the cases into two groups, those in which jaundice was minimal or absent, and those in which jaundice was moderate or extreme. In 17 of the 31 cases there was a low serum bilirubin in the presence of a retention of from five to 30 per cent of the dye. Of these 17 cases, in 13, or 76 per cent, the clinical diagnosis of cirrhosis had been made; and in three, chronic passive congestion due to myocardial failure was present. On the other hand, of the 32 cases in which there was no dye retention, in only one was there clinical evidence of early cirrhosis. It is evident, therefore, that the dye test may well be of distinct service in indicating the differential diagnosis in cases in which cirrhosis is suspected but icterus is not present. In fact, it is in cases of liver disease without marked jaundice that the dye test is most useful.

In cases in which the jaundice is very definite or marked, however, the use of the dye test adds little to the clinical data, as the degree of retention parallels closely the degree of jaundice. In cases of obstructive and catarrhal jaundice with a serum bilirubin of from six to 15 mgs. per 100 cc. there was a retention of from 35 to 70 per cent, while in cases of metastatic carcinoma of the liver with a serum bilirubin of five mgs. or less, the retention was only 20 per cent. This variation in the degree of retention might be of possible benefit in establishing a differential diagnosis, but nevertheless we feel that the chief value of the bromsulphthalein dye test is in cases in which there is no jaundice.

In discussing the determination of serum bilirubin, whether by the van den Bergh or the icterus index method, I wish not so much to prove the value of these determinations—a well established fact—but rather to point out a few of the interesting uses to which they can be put. Jaundice, whether apparent or subclinical, is classified as obstructive, hepatic, and hemolytic. By the use of the van den Bergh reaction hemolytic jaundice can be differentiated from jaundice of the hepatic or obstructive type. It is also believed that a biphasic or delayed reaction indicates that the icterus is hepatic in origin. This point has not

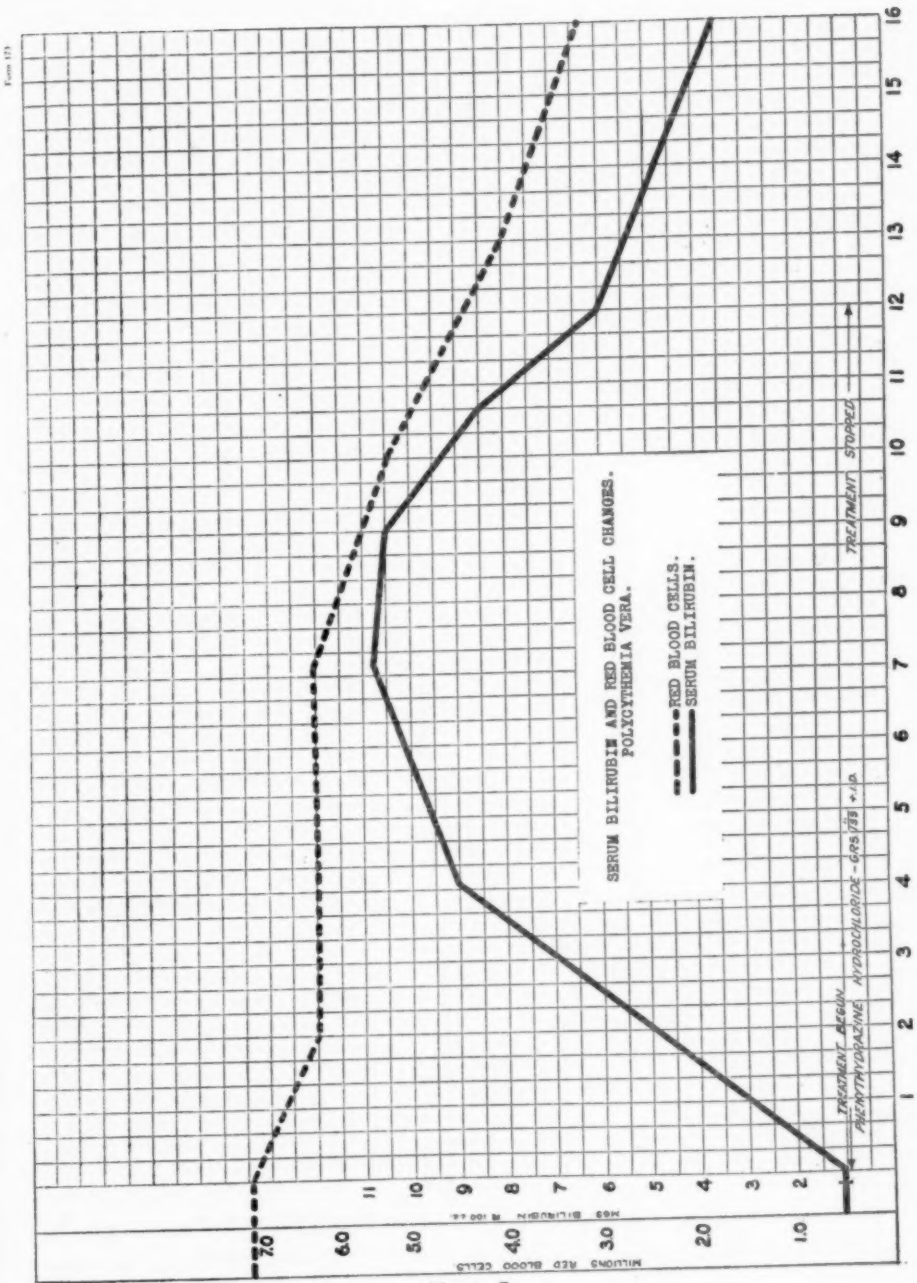
SERUM BILIRUBIN AND RED BLOOD CELL CHANGES.
POLYCYTHEMIA VERA.
RED BLOOD CELLS.
SERUM BILIRUBIN.
TREATMENT STOPPED
TREATMENT BEGUN
PHENYLHYDRAZINE HYDROCHLORIDE - 0.05 GRS/KG + I.D.
MILLIONS RED BLOOD CELLS
MGS BILIRUBIN N 100 CC.

Chart I

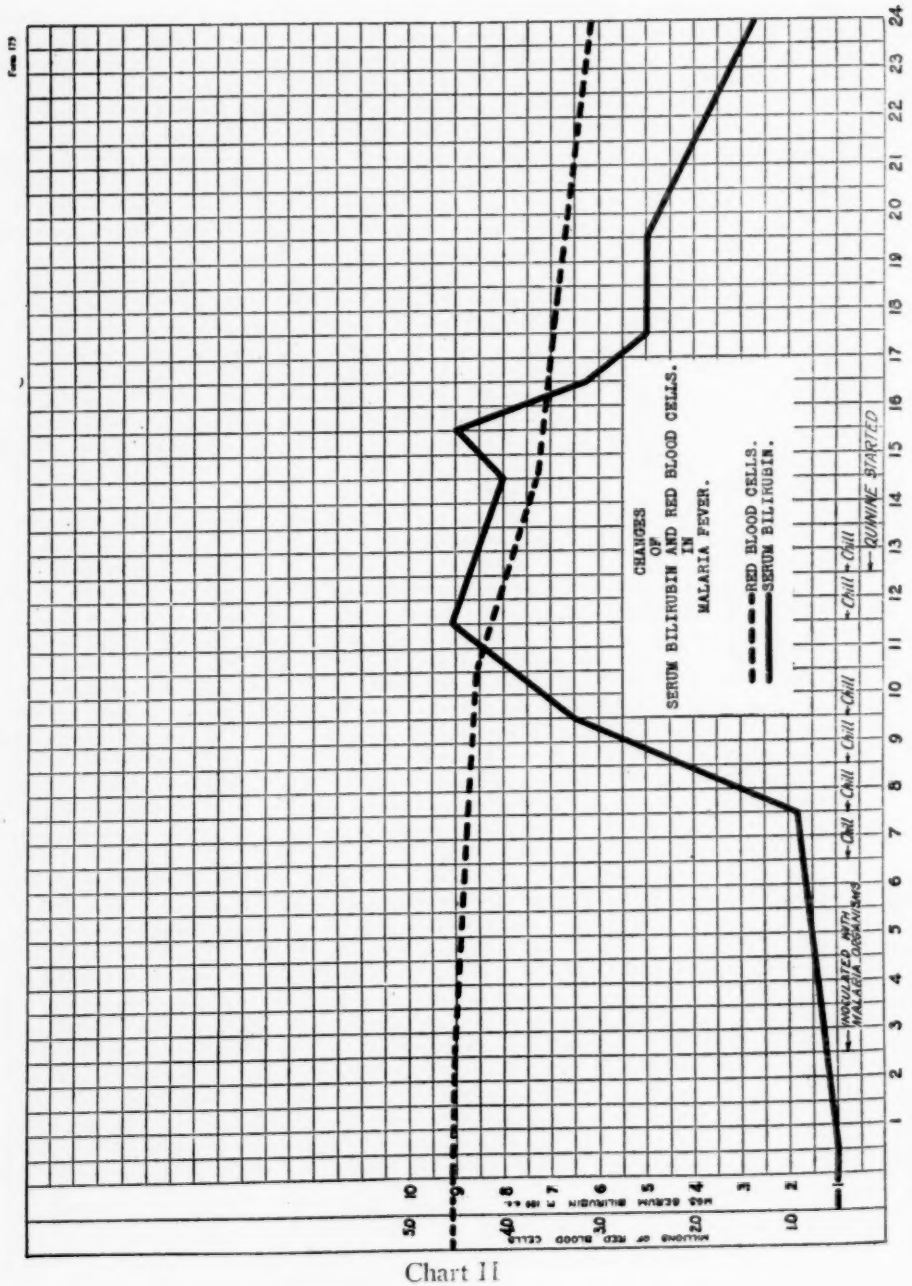
CHANGES
OF
SERUM BILIRUBIN AND RED BLOOD CELLS.
IN
MALARIA FEVER.
RED BLOOD CELLS.
SERUM BILIRUBIN.
INOCULATED WITH MALARIA ORGANISMS
Chill
QUININE STARTED

Chart II

been entirely proved but it is well known that in catarrhal jaundice the bilirubin test gives this type of reaction.

Determinations of the serum bilirubin are definitely of value in following the progress of patients from day to day. This subject has been much stressed, especially by surgeons, who regard the study of the degree of jaundice and its changes as a most necessary factor in the treatment of obstruction of the common duct. From the medical standpoint the study of diseases by this means is also illuminating, and controls in certain instances the course of treatment. The accompanying charts illustrate the findings in successive bilirubin tests in the course of two of the cases in our series.

Chart I illustrates the changes in the serum bilirubin and red blood cell counts in a case of polycythemia vera under treatment with phenylhydrazine hydrochlorid. It will be noted that soon after the treatment is started the serum bilirubin rises rapidly—much more rapidly than the red cell count decreases. It is probable that the circulating red cells are maintained by mobilization of cells from the bone marrow. The van den Bergh reaction is always indirect, showing the hemolytic origin of the bilirubin. This has been very convincing in proving to me that there are two kinds of bilirubin. I have always suspected that the indirect reaction was due to a combination of bilirubin with cholesterol or adsorption in the serum proteins. However, this amount of bilirubin is equivalent to that seen in marked jaundice with obstruction and therefore it shows that the amount of bilirubin is not a factor in the direct and indirect reactions. A clue is also given as to the length of time treatment should be continued. In this case an anemia of 2,500,000 red cells developed, the fall in the cell count continuing for a week or more after the discontinuance of the treatment. No doubt the treatment ought to have been stopped when the maximum blood cell destruction was reached, as indicated by the serum bilirubin.

Chart II illustrates the changes in the bilirubin and red blood cell counts in a case of malarial fever which had been produced in the treatment of general paresis. The chills on successive days are also indicated. This patient became quite ill and because of the marked elevation of the serum bilirubin, the chills were terminated by quinin. The reactions in this case were biphasic and indirect. That is, some color was produced gradually before the addition of alcohol but it was markedly increased by alcohol. Clinically this patient showed evidence of liver disturbance which was probably due to the malarial fever.

Such data add interest to the study of such conditions and in many cases prove of real value in determining the type of treatment which should be employed.

CONCLUSIONS

1. The levulose tolerance test is of slight value in the study of liver diseases.

2. The bromsulphthalein dye test is of distinct value in the diagnosis of liver disturbance, especially in the absence of jaundice.

3. The van den Bergh reaction is valuable in the differential diagnosis of conditions in which icterus is present and in following the course of the disease in such cases.

Urobilin Physiology and Pathology*

(ABSTRACT)

By Philip D. McMaster, M.D., and Robert Elman, M.D., *New York*†

CLINICAL interest in urobilin has always been great, yet at the present day the conclusions confidently drawn by workers with the substance far outrun actual knowledge of it. Analysis of the previous literature makes clear that the hypotheses of the origin of this pigment show no semblance of accord (1, 2). Every conceivable organ and tissue has been championed by one author or another as the sole site of origin of urobilin.

In the course of studies upon the physiology of bile made in this laboratory, methods were described (3, 4) whereby animals can be totally, partially and intermittently deprived of their bile without infection of this secretion or of the duct system. These methods possess obvious advantages for the study of urobilin physiology since they permit a comparison of the effects of total and partial bile loss upon the formation of this pigment. It will be seen too that the absolute exclusion of bile from the intestine, which one of these methods affords, is necessary to any such study. Our work has been carried out with healthy, robust animals having uninfected livers and bile passages, save in a few instances to be mentioned, in which deliberate infection was accomplished for purposes of comparison.

Means were also found (5) to avoid the influence of the factors responsible in part for the inaccuracy of urobilin determinations through the development of clear fluorescent solutions from urobilin-containing urine, feces, and bile obtained from the dog. Conversion of the urobilinogen to urobilin was accomplished during the procedures. Measurement of the urobilin content was effected by comparing its fluorescence at great dilution with a standard containing acriflavine, calibrated in turn against pure urobilin.

Though designed for experimental procedures on the dog, the methods would seem adapted for clinical uses as well. With these aids we have studied urobilin physiology.

Derivation of Urobilin. Relation of the Bile to the Presence of Urobilin in the Body

We have been able to show that the normal presence of urobilin in the bile

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†From the Laboratories of the Rockefeller Institute for Medical Research.

and feces of dogs depends on the passage of bile pigment to the intestine, either through the normal channels, or by abnormal ones, as when it is fed by mouth (4). Complete loss of the bile from the body resulted in the total disappearance of urobilin and urobilinogen from the bile, feces, and urine. Rarely very faint traces remained in the feces, the origin of which was discussed. Partial loss of the bile resulted in a corresponding reduction in the urobilin of the dejecta (4).

Total obstruction of the bile flow caused disappearance of the urobilin of the bile and stool (4). Later as the animals became heavily jaundiced the pigment appeared again in very small quantity in the feces. Autopsy at this time showed that the intestinal mucosa was deeply tinted with bilirubin some of which had undoubtedly passed into the lumen of the bowel and had there been changed to urobilin.

Employment of the "altercursive intubation" (4), by which an intermittent diversion of the bile stream of animals from the intestine to a collecting apparatus could be effected, showed that while bile pigment still reached the intestine urobilin was present in the bile secreted by the liver but that almost at once after the bile had been diverted from the gut urobilin disappeared from it. In relation to this finding it was noticed that in animals from which merely a small fraction of the bile was collected, that from a single liver lobe, while the greater portion reached the intestine there was most urobilin in the bile at times when most bilirubin was entering the intestine.

The earlier work of others has established the fact that urobilin can be obtained from bilirubin, *in vitro*, by reduction (6, 7). That this change takes place in the intestine as well, by the action of bacteria, has also long been known. In recent years (8) experiments upon the method whereby this ordinarily comes about in man have shown that certain of the intestinal flora possess this transforming ability. These factors account for the presence of urobilin in the stool—but what of its presence in the bile?

ABSORPTION OF PIGMENTS OF BILIARY DERIVATION FROM THE INTESTINE

In the course of these studies, dogs losing the total bile as the result of common duct intubation, and in consequence urobilin-free—the bile, feces, and urine containing none of the pigment—were fed either their own bile or urobilin-free bile from similar urobilin-free dogs. All the animals so fed exhibited a great increase of the bilirubin of the bile and urobilin appeared in it (4). From this fact and from others it became evident that urobilin appeared in the normal bile only when bile pigment in some form was allowed to reach the intestinal tract. The evidence pointed to the absorption from the intestine either of the pigment or of substances out of which it might be formed. A closer study of the problem of this absorption has been undertaken. For the purpose pure bilirubin and urobilin have been used and the total bile collected from day to day in a sterile condition

according to the methods mentioned above (3, 4).

Feedings of pure bilirubin by mouth to dogs, like those of whole bile, increase greatly the amount of this pigment in the hepatic bile (9). Control feedings of bile salts, while greatly increasing the bile quantity, cause no change in the pigment output. Instillations of pure bilirubin directly into the duodenum of dogs, appropriately intubated, are followed by pronounced increases in the bilirubin output in the bile (9).

Feedings of pure urobilin to dogs, yielding urobilin-free bile, as result of diversion of the secretion from the intestine, are followed by the appearance of this pigment in the bile (9).

The phenomenon of pigment reabsorption would appear to be far-reaching in its implications. It must be taken into account in any hypothesis of pigment metabolism. The clinical utilization of the urobilin output in the feces as a measure of blood destruction should only be undertaken with the understanding that urobilin is subject, not only to degradation but to reabsorption.

THE FORMATION OF UROBILIN UNDER PATHOLOGICAL CONDITIONS

These experiments have yielded answers to a number of questions of prime importance in urobilin physiology. Together they prove that the existence of urobilin in the stool, and in the bile as well, under normal conditions depends on a delivery of the bile itself, or, to speak more precisely, of bilirubin to the intestine. Here it is changed to urobilin, and thence reabsorbed in part, to be taken out of circulation again by the liver and partly, at least, secreted into the bile.

Urobilin and the Damaged Liver. A variety of evidence was presented (10) showing that these facts hold true even under circumstances of severe liver damage or biliary obstruction when unaccompanied by infection. Animals rendered urobilin-free by collection of all the bile from the intubated common duct remain urobilin-free after severe hepatic injury by chloroform, phosphorus, toluylenediamine and amyl alcohol (10), even when severe enough to cause death.

In our experiments urobilinuria was never found after liver damage except when bile pigment was present in the intestine. Thus, for example, it appeared during the first days after ligation of the common duct, but disappeared as the stools became acholic. When this had happened a small amount of urobilin-free bile, given by mouth, precipitated a prompt urobilinuria. After obstruction of the duct from one-third of the liver, mild urobilinuria was found, but no bilirubinuria. In animals intubated for the collection of a part of the bile only, while the rest flowed to the duodenum through the ordinary channels, liver injury caused urobilinuria, unless indeed it was so severe as to lead to bile suppression, when almost at once the urobilinuria ceased, though the organism became jaundiced (10).

The evidence here presented, when taken with that of our previous papers (4, 9, 10, 11), clearly proves that urobilinuria is an expression of the inability of the liver cells to remove from circulation the urobilin brought

by the portal stream, with the result that the pigment passes on to kidney and urine. Urobilinuria occurs with a far less degree of liver injury than does bilirubinuria.

The Relation between Urobilin and Conditions Involving Increased Red Blood Cell Destruction

Further evidence was presented (11) that the intestinal tract is, under ordinary circumstances, the sole place of origin of urobilin.

Animals rendered urobilin-free by the collection of all the bile from the intubated, uninfected common duct, remain urobilin-free during and after extensive blood destruction caused by intravenous injections of distilled water, as also after reinjections of the animal's own blood, hemolyzed *in vitro*. No urobilin appears in the bile, urine, or feces of animals so intubated when blood destruction has been caused by sodium oleate, or by an agent, toluylenediamine, which damages the liver as well as the blood (11).

On the other hand, when bile flow into the intestine is uninterrupted, urobilinuria occurs during blood destruction caused in any of the ways mentioned and it parallels, both in severity and duration, the destructive process. (11).

Merely increasing the amount of bilirubin within the intestines of healthy dogs by feeding urobilin-free bile, will lead to marked urobilinuria (11). The extravasation of blood into the tissues, resulting from the trauma of an operation for intubation of a bile duct, does not lead to urobilinuria in animals losing all of the bile after this operation, but may do so when only a small fraction of the bile is drained, while the remainder reaches the intestine as usual. The production of artificial hematomas, without operation, is not followed by urobilinuria, under the circumstances last mentioned, but merely by an increase in the bilirubin of the bile. The effect on the liver of the anesthetic employed during the intubation may be responsible for the difference in the two cases (11).

During the course of certain intercurrent infections affecting some of the intubated animals, notably distemper, there was a drop in the hemoglobin percentage of the circulating blood, accompanied by an increased output of bile pigment or further by urobilinuria, when the conditions were such that bile still reached the intestine. The findings pointed to increased blood destruction as a factor in the urobilinuria.

The evidence presented suffices to demonstrate, that urobilinuria, occurring during blood destruction, is primarily the result of an increased excretion of bilirubin from which, in turn, an unusually large quantity of urobilin is formed within the intestine. The liver fails to remove from the portal blood all of the latter pigment which is resorbed and consequently some of it reaches the kidneys and urine.

THE RELATION OF BILIARY INFECTIONS TO THE GENESIS AND EXCRETION OF UROBILIN

The evidence thus far assembled was obtained from the study of animals with uninfected livers, yielding sterile bile. How will the infection of

the liver with urobilin-producing bacteria affect our conclusions? That one may actually produce urobilin *in vitro* by inoculating sterile urobilin-free bile is well known (6, 7, 8). We have been able to accomplish the same thing *in vivo,* for the experimental infection of the intubated and previously sterile biliary tract of the dog with particles of the stools leads to a formation of urobilin from the bilirubin of the bile as it flows through the ducts (12). No urobilinuria occurs, however, unless temporary biliary obstruction is produced, or the liver parenchyma injured. Then urobilinuria develops, despite the fact that no bile is reaching the intestine and, by corollary, no urobilin being formed there.

Cholangitic urobilinuria, as one may term the phenomenon just described, to distinguish it from the urobilinuria having origin in pigment absorbed from within the intestine, is far more pronounced in animals possessing a healthy gall bladder than in those with a pathological gall bladder or with one prevented from functioning by severance of the cystic duct (12). These facts suggest that there may be an active absorption of urobilin from the normal gall bladder. There can be no doubt that the pigment is absorbed from within the bile ducts.

The experiments here described throw light upon the mechanism of a type of urobilinuria previously considered due to the formation of urobilin from the liver cells. Instead of invoking such a parenchymal activity —for which our extensive experiments already reported yield not the slightest evidence—it is now possible to explain the observed facts by the absorption of urobilin produced through bacterial action on the bile passing through ducts and gall bladder. The possibility that urobilin formed in this way, in an infected biliary tract, may be resorbed therefrom and excreted in the urine constitutes, theoretically at least, an extraintestinal origin of urobilinuria. But it must be clearly pointed out that the phenomenon, if it occurs in man, is extraneous, having nothing to do with liver function or with urobilin physiology as such, no matter how important it may be clinically.

The experimentally induced formation of urobilin in an infected biliary tract gives a ready explanation of certain discrepancies between our findings and those of others. In all previous experiments of this nature an open, infected fistula has been present, one infected doubtless with organisms capable of producing urobilin in the bile. Such organisms are present in dog feces and the animal usually has access to the fistula opening. We believe that all of the instances of the supposed hepatic formation of urobilin may be explained in this way.

The fact should be emphasized that only a certain type of infection will bring about the changes described. The biliary tract may be infected for a long time with the ordinary saprophytes or even with pyogenic organisms without any reduction of the bilirubin to urobilin. Some fecal bacteria by contrast are capable of maintaining themselves in the biliary passages for indefinite periods of time, there causing urobilin formation. That some of the urobilin is absorbed our experiments show. The question

whether a manufacture of urobilin ever takes place within the biliary tract of human beings other than those having biliary fistulas is one of much clinical importance. A bacteriological study of infected biliary tracts should be undertaken by surgical pathologists with a view to determining the incidence of urobilin-producing organisms.

There is no evidence whatever to justify the belief that urobilin is ever formed through the action of liver parenchyma. There may conceivably be an intralobular formation of the pigment consequent upon the activity of bacteria within the liver tissue, though such a happening has yet to be demonstrated.

The fact is to be emphasized that urobilin appears only when the bilirubin of the bile is subjected to reduction by certain bacteria. Normally this takes place in the intestine but it may also occur in a biliary tract contaminated with the appropriate organisms. Urobilin in the urine depends, first upon the absorption of the substance from these situations, and secondly, upon the failure of the liver to remove the pigment from the blood.

REFERENCES

(1) Meyer-Betz, F., *Ergebn. inn. Med u. Kinderheilk.*, 1913, xii, 733.

(2) Eppinger, H., Die Hepato-lienalen Erkrankungen, Berlin, 1920, 76.

(3) Rous, P., and McMaster, P. D., *J. Exp. Med.*, 1923, xxxvii, 11.

(4) McMaster, P. D., and Elman, R., *J. Exp. Med.*, 1925, xli, 513.

(5) Elman, R., and McMaster, P. D., *J. Exp. Med.*, 1925, xli, 503.

(6) Maly, R., *Ann. Chem.*, 1872, *clxiii*, 77.

(7) Muller, F., *Verhandl. Schles. Ges. vaterl. Cult.*, January 15, 1892.

(8) Kammerer, H., and Miller, K., *Deutsch. Arch. klin, Med.*, 1923, cxli, 318.

(9) McMaster, P. D., and Elman, R., *J. Exp. Med.*, 1925, xli, 719.

(10) Elman, R., and McMaster, P. D., *J. Exp. Med.*, 1925, xlii, 99.

(11) Elman, R., and McMaster, P. D., *J. Exp. Med.*, 1925, xlii, 619.

(12) McMaster, P. D., and Elman, R., *J. Exp. Med.*, 1926, xliii, 753.

The Clinical Significance of Jaundice*

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THEORIES in the matter of jaundice and ideas, coming from the laboratory or the bedside, that contemplate the physiology and the pathology of bile pigment as anything other than an affair of the liver have never gone far in useful application. Stoppage of the gall ducts or gross abnormalities of the liver are so commonly the cause of jaundice that the liver and its ducts have always been the principal consideration when jaundice is to be explained.

Virchow's (1) demonstration that a strange pigment which forms about extravasations of blood was identical with the bile pigment gave rise to a theory that bile pigment could be formed outside of the liver. This knowledge together with the clinical observation on the relation between anaemia and jaundice gave rise to the old classification into hematogenous and hepatogenous jaundice. A classification useful only so far as it can be applied, but never very useful any more than to say that in the former type the liver is excluded—while in the latter the liver is involved. Minkowski and Naunyn's (2) famous experiment with the goose stood for many years as the final and conclusive proof that without the liver there could be no jaundice—yet clinical medicine was little influenced by the apparent conflict between experimental fact and clinical fancy. The goose experiment in fact seemed incontrovertible and was never repeated until very modern times, and after the birth of the so-called reticulo - endothelial system, when McNee explained the discrepancy by showing that removing the liver from the goose likewise removes the bulk of the reticulo-endothelial system in that particular animal. Eppinger's (3) all inclusive theory that all jaundice is due to bile thrombi in the liver likewise had no profound influence in our clinical thinking, although it endured as a theory for a long time. Present day practice—even "up to the minute medicine"—still deals mostly with the old-fashioned ideas although remarkable new facts are at hand as to the physiology of bile pigment formation and new laboratory technique for the study of jaundice. Chief of the newer methods is the examination of blood for bile pigment—whether it is done by methods of direct comparison as with the Mühlengracht (4) standard or by the Van den Bergh (5) method it is a simple device. The simple un-

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adorned statement of the bilirubin content of the blood will always be useful because it is evidence of an abnormal process. When the Van den Bergh method is used only as a measure it serves a good purpose even though difficult to do, but when the so-called Van den Bergh tests are used to tell us the cause of the jaundice we revert to necromancy, and the reading of oracles.

McNee (6) has recently offered us a rationale for these Van den Bergh tests, and has tried to make them reputable by proposing a theory. The theory begins with the fact that bile pigment is formed outside the liver in the reticulo-endothelial system, and that the epithelium of the liver constitutes a filter membrane with the pigment, born in the bone marrow, spleen and elsewhere on the giving side, and the bile capillary on the receiving side. It regards also the three varieties of Van den Bergh tests—direct, indirect and biphasic, and the well-known orthodox—three kinds of jaundice, that in which the liver is obstructed called hepatogenous, that in which the liver is not obstructed called hematogenous, and unknown forms. The theory assembles all these facts into a homogeneous whole according to a uniform principle as follows—that the direct test is due to bile pigment that has passed through the liver filter and is then reabsorbed, and that the indirect test is due to pigment that has never passed the liver filter, and that the biphasic is due to the both forms combined. Any theory true or false is a good one if it inspires thought and compels work, but this theory of jaundice is a bad one because it leads not at all to thinking or working, but only to the reading of tests. It is doubly bad because the tests do not work. But because these tests are convenient and are backed up by a plausible theory they have taken well in medical practice. The most recent edition of the Osler has given undue prominence to these tests so that the old-fashioned methods of study are slighted. Something should be done about it. This much has been done. Medical literature, particularly that dealing in case reports, frequently shows where the tests have been applied and the experienced clinician has been led seriously astray. These reports are numerous, but too scattered to be cited here. However, the situation is confusing and merits more critical view of the heart of the matter—that is, the experimental basis and reason for the tests. I feel such a discussion is in order here.

Van den Bergh's original observation that there are three kinds of tests —direct, indirect and biphasic—has given rise to the idea that there are three kinds of bile pigment in the blood, as the manifestation of three separate pathological processes. The Van den Bergh test, if you permit me to remind you, is a color reaction between Ehrlich's diazo reagent and bilirubin. That bilirubin reacts in a specific way to develop this color no one has disproved, nor even reasonably denied. It is affirmed that with three different tests we have proved three different substances, but the indirect test you may recall is done exactly like the direct excepting that the blood

plasma is treated first with alcohol in order to develop color.

It is my belief based on experimental work of my own (7) and reported in 1919 under the title "Acholuric Jaundice" that we are dealing in this situation—not with three separate substances, but with in one instance, bile pigment in simple solution in the blood, in another instance with bile pigment adsorbed to the blood protein and in the third instance with mixtures of the two. I came to this conclusion by finding that bile pigment in simple solution passes the kidney filter into the urine and can be made to dialyse from the blood. I have found further that bile pigment which was attached to the protein would not dialyse from the blood and would not pass the kidney filter. I found also that there were mixtures in which there was bile pigment in simple solution and bile pigment adsorbed to the protein in varying amounts. I made further observations that in hematogenous jaundice there was no bile pigment in simple solution, but there was much attached to the protein and consequently none in the urine. I found further that in obstructive jaundice that there was much bile pigment in simple solution, that there was little bile pigment attached to the protein, and therefore much bile pigment in the urine. I supposed then that we were dealing here with different substances and that the study of such findings might lead to the analysis of the more difficult clinical problems. In the end, after applying dialysis to many clinical specimens, I came to the conclusion that the degree of adsorption of bile pigment to protein was not dependent on the pathogenesis of the jaundice, but dependent on purely physical—possibly on physical chemical factors—in the main dependent on those things which modify the absorption of the dye to colloidal substances. To be more exact when bile pigment is dosed into the blood stream rapidly and in large amounts there is much in simple solution and little adsorption to protein, and when bile pigment is dosed into the blood in small amounts and over a long period of time, there is little or none in simple solution, but there is much attached to the protein. In the end, so that instead of giving evidence to the origin of different varieties of bile pigment, I find evidence pointing to the rate and the duration of the staining of the body with a dye. These clinical observations I was able to augment by in vitro experiments with protein and with dye in which I was able to reproduce specimens produced by my patients. Later on with the advent of the literature on the Van den Bergh tests, I found that bile pigment in simple solution in the blood gives a direct test, bile pigment attached to the protein gives indirect test, and that mixtures give the biphasic. I am by no means alone in this idea, nor do I claim priority.

Rich (8) dealing with combination of bile pigment and protein which gives only the Van den Bergh indirect has exposed the blood to a proteolytic enzyme and thereby transformed the indirect to the direct. This experiment I have done myself and, furthermore, have incubated mixtures of pig-

ment and protein so that I have transformed the Van den Bergh direct into the Van den Bergh indirect—more than this Favilli (9) has ligated the common duct of dogs, rabbits, guinea pigs and has found that in this situation the Van den Bergh has passed gradually from the indirect to the direct—sometimes all three forms being present at once. He concludes that the three tests are due to varying degrees of adsorption of bilirubin to protein. Oka T. (10) has done the same thing and came to the same conclusion. Levi and Crailsheim (11) did the same. Rosenthal (12) has gone farther on the same theory and has studied the relation of bile salts to the process of adsorption of dye to protein. He would add the influence of bile salts as another factor in determining the relation of pigment to protein. My own efforts were able to describe only two factors—that is the time and the intensity of the staining process. It is, therefore, timely to point out, from practical considerations as well as critical experimental studies, that the Van den Bergh tests can not answer our questions as to the cause of jaundice. What have we that is any better? Let us see what jaundice means today. The latest work on the formation of bilirubin by Mann (13) and his associates shows very satisfactorily that some other structure than the epithelium of the liver is responsible for the origin of bilirubin. He has gone further and shown that the spleen and bone-marrow—in fact all of the tissues of the reticulo-endothelial system, form bile pigment in considerable amounts. Whether they have shown that bile pigment is not formed by the Kupffer cell of the liver is unimportant. We can safely say with Mann that bile pigment is formed by the reticulo-endothelial system. Farther than this it is unwise to go. Rich has shown to our satisfaction that there is no other source for bilirubin than destruction of the red cell and liberation of hemoglobin. The theory that all bile pigment is formed outside of the liver epithelium, and that the liver epithelium is the organ of excretion, can be readily accepted and harmonized with all of our clinical experiences to date. This theory can be pushed to its logical conclusion. We can consider jaundice then as a reaction between a dye substance and the colloids and water of the body. Ordinarily this dye substance is eliminated by way of the liver, but there is a normal amount always present in the blood. This amount is variable in individuals and fluctuates with the taking of food—being increased by fasting and diminished by digestion. By definition this normal amount never increases to the point of becoming jaundice. Precisely how in any instance this normal pigment becomes increased to the degree of being visible as jaundice is not known and need not be known. We can, without further theorizing, estimate the amount of bile pigment in blood, in urine and stool, in many simple cases of jaundice and from that hope to understand the more complex problem. The most satisfactory method for the blood is the direct comparison with an artificial standard of potassium dichromate — after Meulengracht. Carotin

is the only substance that seriously interferes with this method, but carotin jaundice is easily disposed of by being recognized by its distribution in the body. Carotin stains mostly the thick skin of the palms and soles, and does not stain the sclerae—while bilirubin icterus does just the opposite. Urobilin is not a colorful substance and causes no jaundice. Bile pigment in the stool is present usually only as urobilin and the method of McMaster (14) or that of Wilber and Addis (15) is satisfactory. The urobilin content of the stool is a good guide to the bilirubin output of the liver. Urine can be measured by the method of Whipple and Hooper (16) and results are accurate enough for comparison in well conducted case study. It is true that these laboratory methods are troublesome, but the end results are useful. They have this virtue in that they are of the staining process known as jaundice—they are not tests applied to seek out certain disease entities. With this method of study it is perfectly obvious that patients with obstructive jaundice have increasing amounts of bile in the blood and urine, but none in the stool. It is obvious that patients with so-called hematogenous jaundice have much bile in the blood—much bile in the stool and little or none in the urine. When sufficient number of cases of jaundice that can be acceptably classified are studied so that we understand them and know what to expect as to the amount of bile pigment in the blood, urine and stool, we can then approach the unclassified with a well tried method and learn just what is happening in the way of bile pigment formation, distribution and elimination. There is no proof in laboratory studies that absorption of bilirubin from the intestine ever occurs in significant amounts, and no clinical experience that suggests such a mechanism. There is good evidence from experiment and from the clinic that bile pigment after being converted to urobilin is reabsorbed—and that such reabsorption serves to accomplish the formation of bilirubin anew. There is in all likelihood absorption of both bilirubin and urobilin from the gall bladder into the blood or lymphatics. There is good reason to believe that bile pigment can find its way into the intestine by way of the blood—when ducts are obstructed—but only when there is much in the blood and then sufficient amounts leave the blood to produce small traces in the stool.

There is but one way to increase the total output of bile pigment or to augument the product of the reticuloendothelial system—and that is by increasing blood destruction. Rous and Brown (17) have shown that after violent exercise there is loss of red blood cells and increase in bile pigment. The well known fact that the stools in pernicious anaemia contain an enormous excess of pigment is another statement of the same condition.

Even though bile pigment output is the result of red blood cell destruction, daily estimates of bile pigment cannot be taken as the index of red blood cell turnover. The methods are not accurate enough and too many variables are uncontrolled. Studies in total bile pigment output are useful in

classifying the anaemias even when no jaundice is present.

From my own studies in the ordinary and well known forms of jaundice I can generalize as follows—that in catarrhal jaundice, in the early stages, there is a period when bile pigment is excluded from the intestine and increases in amount in the urine and in the blood. Coincident with the reappearance of bile pigment in the stool there begins to be a diminished amount in the blood and in the urine. At no time is there any striking increase in the entire output of bile pigment in a way to suggest an over production.

Biliary colic resulting in obstruction of ducts may be followed in eight to twelve hours by icterus of the plasma; further, colic can occur without any demonstrable icterus; that icterus is less likely to result from obstruction of short duration if the gall bladder be normal. When the gall bladder is no longer able to function icterus results in shorter time after obstruction. In Laennec's cirrhosis, I have found that on rare occasions there is diminished amount of bile pigment in the stool coincident with decreasing amounts in the blood and urine. Some patients in this group show relatively little bile pigment formation and for several weeks may have moderate jaundice, with little bile pigment in blood, urine and stool. Following this period of diminished pigment output, there is a period of increasing jaundice with increased amounts in blood, urine and stool. In lobar pneumonia bile pigment has been found to be increased in the stool at the same time that it is increased in the blood and in the urine. Strange to say, there is no demonstrable anaemia following this apparent over production of bile pigment. In pernicious anaemia bile pigment has been greatly increased in the urine, and in the stool simultaneously, but present only in the urine in the form of urobilin. This great increase is never found in any form of secondary anaemia.

These generalizations are not final —they are subject to revision as more work is done, but we think that as long as jaundice is no better understood we should stick to measurements and not go in for tests. All this discussion can be briefly summarized as follows: Until the pathology of the liver and the reticulo-endothelial system is better understood, jaundice should be regarded only as a symptom and not a disease entity—it should be measured only and not tested for.

Present day views of bilirubin physiology are in all probability correct as announced, but no new methods of study are as yet good enough to displace the old.

The Differential Diagnosis of Gall Bladder Disease*

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THE gall bladder must be considered as an integral part of the hepatoenteric system. We must think of the liver as one unit and the intestinal tract as the other unit, the two associated by connecting links which the French call the hepatoenteric circulation. This conception is vitally important, as it emphasizes the complete dependence of one link of the chain on the other portion, the afferent chain connecting the digestive tract to the liver and the biliary tract, the great efferent chain. The liver, like the kidneys, is to a large degree the excretory organ. The biliary tract is the transit system for bile, and the gall bladder is a diverticulum in the course of this transit system. It certainly plays no very active part in upper abdominal digestion. The lack of the organ in many animals and the comparatively unimpaired digestion which occurs in individuals who have been submitted to cholecystectomy bear out this view.

Twenty years ago the diagnosis of gall bladder disease was confined to those cases with biliary colic and sharply circumscribed pain in the upper right quadrant. Today, owing to modern methods and by a more perfect correlation of surgical and medical material, the refinement of the biliary tract diagnosis has approached that stage where it is possible to assume that many forms of gall bladder disease do not present this classical picture. Before discussing my own experience, I would emphasize these fundamental facts regarding gall bladder disease as I see them.

(1) Gall bladder disease is an effect rather than a cause; a result rather than a provocative agent in many of the cases which we encounter.

(2) It cannot be divorced from the central hepatoenteric system of which it is a link or chain.

(3) The gall bladder may be considered as an actual functioning diverticulum in the afferent transit system from the liver to the bowel.

(4) Gall bladder disease rarely exists alone. There is an abundance of clinical and surgical evidence to prove (1) that the liver is usually implicated. Graham, Judd, Heyd and Kilian and MacNeal, and Tietze have emphasized and proved beyond a doubt that liver disease is a common association of biliary tract disease. Sudler goes so far as to contend that there is lymphatic drainage both ways, from the gall bladder to the liver and

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vice versa. One need only to read the admirable brochure of Heyd and MacNeal to be convinced that cholecystitis is only part of a generalized chronic infection. (2) Cholecystitis is frequently associated with a certain degree of pancreatitis. Of 1,290 cases reported by Judd 347 or 26.8% had associated pancreatic disease; and Piersol and Bockus present evidence to show that in 85% of gall bladder disease there was a reduction in over 50% in the amount of one or all the enzymes. (3) The colon is nearly always affected in some way. This is confirmed by both X-ray and clinical evidence; (4) and in the great majority of instances, the portal system is involved. This means that apart from hematogenous infection with the implantation of specific organisms and the contiguous lymphatic association, the contention of Chauffard is not so far wrong. He points out that the sequence of events in biliary disease and cholelithiasis is (1), the character of the bile will in a sense dominate gall bladder function; (2), the condition of the liver cell will dominate the characteristics of the bile; (3), the condition of the portal blood will dominate the condition of the liver cell; (4), and finally, the status of the digestive tract proper from the stomach to the colon will determine the status of the portal blood. Apart from focal infections and contiguous inflammations this sequence of events with its multitudinous possibilities would seem to dominate the biliary tract.

II

Gall bladder diagnosis two decades ago consisted in a well taken history and a careful examination. Today it consists of the same procedure amplified by methods which throw more or less direct light on gall bladder function and pathology. We have at our disposal the following methods:

(1) History
(2) Physical examination
(3) X-ray examination
(4) Duodenal intubation
(5) A study of blood serum, notably the Van den Bergh reaction, the icterus index, blood cholesterol and so forth. To these are appended the separate studies necessary to crystalize a diagnosis in any of the adjacent organs.

Let us consider for a moment the history. A history of biliary colic or sharply defined upper right sided pain more or less circumscribed to the biliary region and in the right upper quadrant is encountered in the majority of cases.

Pain in gall bladder diseases, according to Rolleston, is due to two factors: first, acute inflammation of the gall bladder per se, and second, muscular spasm set up by the presence of the calculus in the duct. The pain in cholecystitis varies according to whether or not there is a stone attempting to pass along the cystic duct. When there is a stone, the pain is generally localized to the region of the gall bladder, or if there be contiguous peritonitis, adhesions, or bands (as is not uncommonly the case) the pain may be diffused over the right side, and even to the chest or to the left side. If the liver and gall bladder are much enlarged downward, the pain may extend down to the iliac fossa

and even down to the lower extremities. When there is a stone in the neck of the gall bladder or in the cystic duct, the pain radiates also to the area beneath the inferior angle of the right scapula. This corresponds to the level of distribution of the eighth dorsal segment from which the gall bladder derives its main nerve supply. In uncomplicated cases, pain is not felt in the right acromial or clavicular regions, but in the right hypochondrium or in the epigastrium alone.

That areas of hyperesthesia do occur in acute biliary disease was well borne out by the findings of Livingston, who emphasizes tests for local cutaneous hyperesthesia as part of a routine physical examination for the diagnosis of acute biliary disease. Of his 50 cases, with but two exceptions all tested patients had positive cutaneous hyperesthesia. Of the two negative patients, one had both gall and kidney stones as concomitant findings and positive skin findings for nephrolithiasis was obtained. The other patient did not have acute colic but merely an increasing jaundice due to a stone.

In a review of the literature, we have arrived at the conclusion that pain in gall bladder disease is as variable as the pain in appendicitis. In other words, the pain may vary from an anginal type to one resembling that of a retroversion.

We note, however, that catarrhal cholecystitis gives a different story from pericholecystitis, that stones in the gall bladder, cystic duct, common duct and ampulla evolve differently. I realize in presenting statistics before this association that they are medical and not surgical and they are open to the serious criticism that pathology may not exist; but right here I maintain that the surgeon demonstrates gross pathology but has no means on the operating table of demonstrating the functional disturbances and incipient pathology which must be present in the large number of cases. He can scarcely believe the findings of Heyd, Tietze and others, who demonstrate histological liver changes when before his own eyes no such change was apparent. According to my own files I have diagnosed some form of gall bladder disease in the last five or six years in over six hundred cases. In going over a consecutive series of 200 cases in which I selected localized circumscribed tenderness over the gall bladder as a subject for analysis, selecting the first 200 cases in which this symptom was clearly presented and accompanied by other signs of biliary disease, in 59% the history was that of typical colic or clean-cut epigastric pain along the right costal margin. In other words, in 59% there was the clinical history concerning which there was very little doubt regarding the diagnosis; in 5.5% the patient complained of burning, showing little or no relationship to the ingestion of food; in 21% the dominating symptoms were those of toxemia with headache, nausea, vomiting and dizziness, and a subsequent survey revealed disease of the gall bladder occurs atypically; in only 5.5% was the evolution of the history such as to suggest the serious problem of an ulcer of the stomach or duodenum;

in 2% of this number there was an absolutely typical migraine; in 3% of the cases the character of the symptomatology was such as to seriously suggest angina; in only 1.5% of cases was there clear left-sided pain which is often explained by a pericholecystitis. In other words, in 41% the symptomatology was atypical and there was evidence to indicate the presence of gall bladder disease. Akana, Greveley and Farr in the study of pain and gall bladder disease note in the great majority of cases pain in the typical site in the right hypochondrium, in 78.4% of cases, with a radiation to the shoulder and back in 28.9%, but the physician sees cases of gall bladder disease in which pain plays no sign. In fact, in our series 10 cases presented were without any sign of pain, but a survey revealed gall bladder disease. In every one of these cases reported there was localized tenderness. In 121 or *0.5% there was diffuse constipation; only 10 or 5% had pronounced looseness of the bowels; 34 or 5% had either the picture of colitis or normal movements; in 45% the appetite was conserved; 24% or so fair; 31%, poor or gone. In nearly all cases after an attack the appetite disappeared for a period. In practically every single case gas usually of the aerophagic type played an important role, in some cases an extremely persistent role. Outspoken jaundice was found in 29—14.5% of this series. The point which I wish to make is to my mind in a certain group of cases gall bladder pathology indicates itself to the clinician with localizing symptoms; with another group it is associated with toxic disturbances incident to disturbed intestinal or hepatic function of which it is only a part; and finally there is a psychology to the gall bladder case with insomnia, wakefulness usually at 2 o'clock in the morning, and restlessness so that 74 or 37% of the cases which we saw had disturbed sleep or were troubled with insomnia. This association was pointed out by Parturier. The typical history and the atypical history of the type just mentioned, but more particularly the chronic upper abdominal invalids whose symptoms show no direct or synchronous association with the gastric digestive cycle can be viewed as gall bladder suspects. One of the most interesting things to me is the cardiac association, varying all the way from palpitation, tachycardia, mild flutter, arythmia to definite angina. Several of these patients were subsequently known to have anginal manifestations. The important point, however, is that angina can be associated with biliary pathology, a very important point to determine. In 71 (35.5%) of all the histories that we went over there was evidence of some cardiac consciousness of the type mentioned. The cardiac association has been pointed out by W. J. Mayo. He also insists upon the widespread effect of biliary disease in producing renal and arthritic symptoms as well.

We then turn to the physical examination. Nothing to my mind is more suggestive than residual tenderness at or near the tip of the ninth costal cartilage and more pronounced on upward pressure. This is enhanced by a fluoroscopic examination by which

it can be definitely demonstrated that tenderness is outside of the duodenal shadow. Unless the attack is recent and the symptom diffuse, tenderness is often fugitive, but residual circumscribed tenderness after an attack is of the most value. A palpable tumor of the gall bladder is, as Mateer and Henderson have pointed out (1), empyema; (2) hydrops, usually associated with stone in the cystic duct; (3) carcinoma; and (4) an occasional gall bladder filled with stones. Rigidity of the upper right rectus, cutaneous hyperesthesia localized to the gall bladder area as Livingston has described are of value. Operation and cholecystography show the variations in gall bladder position, and enhance the value of tenderness outside of the duodenal shadow on fluoroscopy. It is needless to point out that palpation will determine the presence of physical signs over the colon, evidence of the possibility of appendicitis, and the possibility of a right renal lesion as a cause for symptomatology.

I place X-ray examination third because X-ray study usually establishes the anatomic diagnosis, while duodenal intubation like gastric analysis is in a sense a study of impaired physiology. The X-ray study of the gall bladder as carried out today includes three procedures: (1) flat plates; (2) indirect signs; (3) cholecystography. I can recall that 10 years ago I found only 23% of demonstrable gall stones were visualized on the X-ray plate, but by the use of modern technique, better instruments, the Bucky Diaphragm, and double intensifying screens, the percentage of visualized stones or visualized gall bladders is very much higher. There are naturally differences due to technique which vary in different parts of the country. Furthermore, there are several methods, each of which has its adherents in the performance of this procedure. I still believe that a visualized gall bladder is not a normal gall bladder even though it is not a surgical gall bladder.

To me the indirect signs which are frequently observed in gall bladder disease are of great importance. A host of observers, George, Carman, Holzknecht, Kilian, Belden and others, have pointed out the effect of a gall bladder lesion on the associated gastroduodenal shadow. To me the most important are: (1) tenderness outside the duodenal shadow, upward and to the right. In this series that I studied practically every individual presented this symptom; in fact, I doubted the diagnosis if deep palpation revealed little of importance.

(2) An adhesion deformity, fixing the second portion so that its course follows an abnormal deviation to the right, and gives the impression of being fixed along the lower border of the liver or to the gall bladder region. All varieties of duodenal defects can be encountered from fixation, looping, and marked structural defects.

(3) Adhesion defects with saw-tooth serration of the superior margin of the duodenal cap.

(4) A variation of this is looping between the first and second portion of the duodenum before mentioned, but at operation this finding may be encountered when the duodenum is

attached anteriorly to the gall bladder, and the gall bladder may be normal. I have seen this occur on several occasions.

(5) A pressure defect of the duodenal bulb, smooth, well defined, and indicating according to Belden that the tension in the gall bladder is greater than the normal gastric or duodenal tension, which is the reverse of health. This finding, if present in serial photographs, suggests extraduodenal pathology, usually gall bladder.

(6) Permanent distortion of the duodenal bulb, either through spasm or displacement on its axis is far more common in gall bladder disease than it is in ulcer of the duodenum.

(7) Defects of the second and third portion of the duodenum may mean diffuse inflammation of the upper right quadrant resulting in adhesion formation, partial duodenal stenosis, and even diverticular formation owing to fixation at two different points seen in extensive pericholecystitis and in my own experience even more frequently after the operation of cholecystectomy. Adhesion defects involving the pylorus, pyloric antrum, hepatic flexure or beyond this point produce the so-called pseudohepatic flexure of George and are all significant diagnostic points of pathology in the upper right quadrant, most often pericholecystic in origin. In this series of studies of 200 consecutive cases there was an abnormal, or fixed or unusual arrangement of the duodenum in 49 cases or 24.5%; there was a defective cap in 23 (11.5%); there was marked spasm of the cap in 8.5%; there was distinct looping in 6 or 3%; there was angulation and lateral fixation pronounced in 9 (4.5%); there was distinct diverticular formation in 3 or 1.5%; and there was a typical pressure defect in 6 (3%) of cases, and in a larger number where the defect was by no means so pronounced; in 8, (4%), there was definite fixation of the hepatic flexure of the colon; and in 2 cases there was the pseudohepatic fixation of George.

Regarding the stone shadows which are encountered Rowden, quoted by Moynihan, gives these as follows:

(1) "opaque and solid"

(2) "The new moon" or "crescentic type"

(3) "the wedding ring" shape from later calcium deposits

(4) "the mosaic" due to overlapping

The third method of X-ray diagnosis consists in the visualization of the gall bladder by means of a dye. This study to my mind is one of the most helpful in the entire category of diagnostic aids. The Graham test as evolved by that distinguished observer is in my judgment without a question one of the great discoveries of this present contemporaneous era of medicine. I can do not better than to refer to the last and most recent communication by this author, which I believe shows without a doubt the present status of this test. It is considered a routine in the complete investigation of any suspected gall bladder case. I am sorry that I cannot contribute to the already large group of statistics. I have already a number

of cases. I inquired just before I left as the number of cases which had been examined in the Jefferson Hospital in Philadelphia. I was informed that since June 15th, 1926, six hundred cholecystograms had been performed. To my surprise only 22 were operated on, all but one out of the 22 having been correct. Before I left Philadelphia I added another to that number, a positive cholecystogram with definite cholecystitis at operation. "Graham in a recent article (Surg. Gyn. and Obst., Feb. 1927, vol. xliv, No. 2, p. 153) discusses the present status of cholecystography. He points out that this method provides a means of investigating the only functions of the gall bladder which are known at present, namely, the ability to concentrate its contents as revealed by an increasing density of the shadow and the ability to store bile as shown by changes in the size of the shadow. It is not only useful in diagnosing cholecystitis, but it has been of importance in recognizing many more cases of calculi than have been possible by the ordinary X-ray examination; by revealing pericholecystitis and pericholecystic adhesions by positively identifying shadows seen on the plain film as being related to the gall bladder or not; and of showing the various anomalies and abnormalities such as diverticula, double gall bladder, and so forth. He points out that in his own experience a total of 1246 patients were examined by this method. The gall bladder was removed and submitted to microscopical examination in 147 cases. In 143 of these 147 cases the X-ray diagnosis was confirmed, showing a percentage of correctness of 97.28%. He gives a table recording the cases reported in which the cholecystographic examination has been confirmed with operative findings. The oral and intravenous methods are also mentioned. This table shows a percentage of correctness in 446 cases of all authors in the diagnosis of pathological gall bladders to be 97.8%; the percentage of correctness in 115 cases of all authors with a diagnosis of normal gall bladder equals 74; the percentage of correctness in 380 cases by all authors by the intravenous method is 95%; a percentage of correctness in 181 patients of all authors by the oral method equals 89%. Graham points out that he still feels that the gall bladder empties itself of its contents through the cystic duct by washing out its contents by bile from the liver, by the elasticity of the contractile mechanism of its walls, and by variations in intra-abdominal pressure."

More difficult to interpret are the poor shadows and delayed evacuation. I am convinced that a positive cholecystogram can be converted into a negative cholecystogram by medical therapy. I am also convinced that there are variations in response dependent entirely upon non-surgical functional alterations in the organ. I am also convinced that the Boyden meal will induce a greater reduction in the shadow than duodenal intubation and stimulation.

Duodenal intubation is now a standard method of biliary tract investigation. Thanks to my colleague, Dr.

Lyon, it is possible to segregate the bile which is obtained by this method in such fashion that a reasonable clinical interpretation can be attached to the finding. Even before this method was routinely used I studied the duodenal secretion for evidence of biliary mal-function, but I feel that it is important to attempt segregation of specimens in the hope of obtaining definite results. My objection to some of the critics of this method is that they fail to carry out the test in the proper way. It is frequently impossible to obtain on a single examination sufficient stimulation on the first application. I have repeatedly seen four to five tests of the duodenum reveal pathology in only one or two of the aspirates. Furthermore, those who carry out this technique must be familiar with the characteristics of the duodenal contents in health. I believe this is one of the most important things most men fail to do. They must also be informed as to the rationale of the sequence of bile after stimulation. It is likewise essential for the hospital internist or the technician to study normal duodenal contents before the pathological are encountered. While I do not agree with Lyon in all his contentions, I agree with the fundamental principles. I personally feel the necessity of the careful correlation of all data, and to me the microscopy of the bile is the most important, the color sequence of relative importance, and the bacteriology unless associated with pure cultures and plain evidence of infection, the least important. The latter is evident from a more recent study by Judd, Mentzer and Parkell. There is a frequent discrepancy between duodenal cultures and cultures from the bile in the gall bladder. What makes gastric and duodenal cytology so difficult is the more or less constant swallowing of oral secretion. Jackson believes that the principal function of the esophagus next to food transit is the swallowing of saliva, many ounces of which are daily assimilated in this way. I believe:—

(1) That leucocytes increased, clumped and stained are practically always evidence of inflammation or infection, depending upon the particular increment involved, they may suggest trouble in that segment.

(2) The presence of characteristic rows or layers of fan-shaped rosy collecting or columnar bile duct epithelia if pigmented, and when associated with the above are extremely suggestive of angiocholitis or even cholecystitis. They differ from duodenal epithelia in that the latter are cuboidal or ovoidal in type.

(3) Crystals, more particularly cholesterol crystals and the so-called calcium bilirubin type, but particularly the former are evidence of biliary stagnation and I believe evidence of potential gall stone formation. In two cases I had operated on in which no stones were found, this finding was constant, one of black, tarry bile with a puree of cholesterol crystals was found. Lyon believes that in cystic duct obstruction no B fraction is obtained and it is accompanied by the discharge of characteristic flocculi of yellowish brown mucus in shaggy, slimy amounts, often twisted by the

rifling of the cystic duct and encrusted with bile salts; and finally, the presence of bright yellow oleaginous material which melts out into globules, pools or lakes, particularly if the slide be heated; and a lack of normal B bile may mean cholecystitis, adhesions, stone impaction, stricture, and angulation of the ducts.

Finally, I believe that the amorphous material obtained by ordinary drainage, and not produced by the spurt of acid gastric juice, is very significant. Recent studies of our own suggest that there is a high melting-point fat in this amorphous material, and it may be significant as the crystals mentioned above, as an indication of potential stone formation.

Duodenal intubation to me is a physiological study of the biliary tract togethed with an attempt to demonstrate pathology by cytologic means. I can realize its dangers, but I feel it simply adds one more link in the chain of evidence. I believe that chronic biliary disease was usually associated with a disturbance in the gastric secretory output of the downward type. In this group 37% showed a total acidity over 60 after an Ewald test meal; 21% showed an acidity between 40-60; 42% below 40. It is therefore apparent that a reasonable high percentage have not only an intact secretion but an exaggerated secretion. The interpretation of this finding will of course be dependent upon the associated pathology.

Time does not permit me to mention the value of the study of blood in gall bladder disease, but most clinicians are today interested in the quantitative determination of serum bilirubin in demonstrating latent jaundice as revealed by the Van den Bergh serum reaction and the icterus index. I believe that obstructive jaundice in order of its evolution is exactly as Heyd has mentioned:

(1) gall stones
(2) angiocholitis or catarrhal jaundice
(3) cancer of the liver
(4) cirrhosis
(5) cancer of the ducts and gall bladder
(6) cancer of the pancreas
(7) gastric and duodenal cancer

The presence of colicky jaundice with acute biliary obstruction and acholic stools is too well known, but as Haggert points out the characteristic diagnostic symptoms of common duct impaction by stone are:

(1) colic
(2) sepsis
(3) intermittency
(4) chronicity, and to which I would add
(5) a negative cholecystogram
(6) a direct Van den Bergh reaction
(7) acholic stools

and the general urinary and skin manifestations. In the majority of common duct obstructions by calculus, as Courvoisier points out, the gall bladder is atrophied. It is interesting to mention in this connection the study of the circulating blood for cholesterol was tried out by us some years ago in the hope that hypercholesterolemia might offer an efficient differential diagnostic aid in gall stone cases. We had a series in which the cholesterol

content was distinctly increased, but I can recall the first operative case where this finding was not present. The patient had only 166 mgm. Shortly after that another case came to operation with the same finding, and we gave up that method of investigation. To my mind today the situation is very much clarified. It is my belief that at some stage in the evolution of the cholesterol stone there had been an increased blood cholesterol. We now know that an increased cholesterol content can occur for periods of time followed by a distinct diminution. A study of blood cholesterol, therefore, simply indicates the existing content at the time of testing.

In the differentiation of other conditions from gall bladder disease I would name the following as the most important:

Gastric disease is differentiated (1) in the history by the fact that the gastric symptoms usually occur at a definite period in the gastric digestive cycle. (2) The physical signs are rarely localized over the gall bladder unless there is associated pathology. (3) The gastric analysis of duodenal ulcer, from which the differential diagnosis must so frequently be made, shows a different sequence, and in my experience 78% of duodenal ulcers give a characteristically high climbing curve and 96% give a characteristic defect on X-ray examination. Finally, if the X-Ray study of the stomach is negative and also the gastric analysis, flatulent indigestion, symptoms showing no relationship to the gastric digestive cycle, distress and discomfort persisting in spite of gastric therapy, night pain rather than day pain, are all suggestive of biliary rather than gastric pathology. In the differentiation of duodenal ulcer and duodenal diseases, most of these conditions show a certain sequence to gastric digestion. This is particularly seen in the characteristic sequence of duodenal ulcer. Most important are the gastric findings already mentioned. Unless there is periduodenitis the cap is usually movable and the defect is more or less characteristic. The history, gastric analysis, and the X-ray findings will usually enable one to make the differentiation.

Regarding pancreatic diseases, my own experience tells me that this diagnosis is most frequently made by an examination of the movement and by the pressure defects which occur on the X-ray study. In my experience, pancreatic disease most frequently produces a rather characteristic failure of assimilation of fats, and not infrequently of proteins and carbohydrates in the stool. It also produces a pressure defect, flattening out the duodenum when the head of the organ is involved, or producing a pressure defect on the stomach. The value of duodenal intubation and a study of the duodenal ferments to my mind has not yet reached that stage where it is possible to make an early diagnosis. We spent two years studying the ferment activity of the duodenal contents, and I regret to say that our conclusions except in rather advanced disease were not satisfactory. However, this is of value and might be combined with fecal studies.

The study of the liver includes not

only the history, the physical examination, the X-ray determination, but a series of functional tests, most of which throw some light on one of the various functions of the liver. A large number of tests have been devised, but most clinicians are content to study the blood chemistry, determination of segregation of dye with tetrachlorphthalein, the study of C bile or liver bile, and the feces, and if necessary perform the ordinary carbohydrate tolerance tests. Many other tests have been devised but unfortunately do not throw light on the total function of the liver.

Among other differential diagnoses which must be made are those which separate angina, renal stone, enterospasm, chronic appendicitis as well as lead colic. As I have already mentioned, cardiac manifestations are very common in gall bladder disease, amounting not infrequently to actually a form of pseudo-angina associated with marked aerophagia, probably a vagus phenomenon. On the other hand, I have seen angina associated with gall bladder disease, and I feel in every case of angina one should carry out the routine tests such as duodenal intubation and cholecystography to determine the efficiency of this organ. The tendency of angina to become aggravated on effort, the evidence of vessel sclerosis, myocarditis, and the studies of the cardiologist will make this differentiation. In some cases it can almost be mimicked by gall bladder disease. Tabetic crises call for a careful examination in every instance of the reflexes, pupils, blood chemistry, and if necessary examination of the spinal fluid. These attacks can be fulminating and I have seen them mimick almost exactly a severe attack of biliary colic. Renal stone may produce severe pylorospasm, hypersecretion, nausea and vomiting, and resemble biliary colic. A study of the urine, the associated urinary phenomena, the fact that the symptoms predominate posteriorly rather than anteriorly, although this is not always the case, and a plate of the renal region will usually clear up the diagnosis. Patients have been operated on for enterospasm, which in my experience is a very common association of gall bladder disease. In 34 of these cases there was very pronounced enterospasm amounting in some cases to a spastic bowel obstruction. In the great majority of cases of gall bladder disease at some time or other there is associated spasticity of the left side of the bowel; constipation is usually spastic in type. In a careful survey using the above methods, however, the spasm will be evident, and where there was a reasonable doubt and the cholecystogram is negative, particularly in that small group of cases where there is lower left-sided pain, a colon injection will usually clear up the picture. Appendicitis, particularly when retrocecal and pointing upward, can give rise to a great deal of trouble. The roentgenological study of this region, particularly the late plates after the cecum has emptied, will often be helpful. The nature of the attacks, the localization of tenderness, the demonstration of normal findings in the gall bladder region, will usually make the differentiation. However, one must realize

that chronic appendiceal and gall bladder disease are very frequently associated. Lead colic is mentioned as a cause. However, the condition of the red cells and the blue line on the gums, the history of the ingestion of lead, and the general spasticity of the colon, will usually make the differentiation.

It is my belief that wherever gall bladder disease is suspected it is wise to carry the patient through the entire group of procedures, beginning with duodenal intubation, following through with a complete X-ray study and finally the blood serum and even the movement. I feel satisfied that a careful study of this type including these various procedures will in most instances enable the observer to make a correct diagnosis. As internists we must realize, however, that gall bladder disease is frequently associated with colon disease, chronic appendiceal disaese, chronic liver disease, pancreatic disease, heart disease, arthritis, and severe secondary anemias. It is therefore apparent that in this large group of clinical conditions a survey of the gall bladder is an important part of the complete study.

Roentgenographical Aspects of the Differential Diagnosis of Disease of the Gall Bladder*

By B. H. Nichols, M.D., *Cleveland Clinic, Cleveland, Ohio*

THERE is no more fertile field for the roentgenological study of pathological conditions than that presented by the upper right abdominal quadrant. It is the uncertainty which attends the diagnosis of lesions within this area that has for so long demanded the exploratory operation. This is well illustrated by the finding in a recent survey of the cases of hydronephrosis of the right kidney seen at the Cleveland Clinic that in thirty per cent of these cases an exploratory operation had previously been performed for a supposed gall-bladder lesion or other abdominal disorder. The time has now arrived, however, when every patient with clinical symptoms referable to the right upper abdominal quadrant has a right to demand an accurate diagnosis, this assurance being largely due to recent developments in the field of roentgenology, principal among which are duplitized films, the Bucky diaphragm, and the use of opaque substances for the study of the abdominal viscera. Today, by a systematic roentgenographical study in the light of the clinical history presented in each individual case, the differential diagnosis can usually be established.

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In the investigation of the right upper abdominal quadrant our usual procedure is first to take a film of the kidneys and lumbar spine. This enables us to exclude or to determine the presence of a pathological condition of the spine, such as Pott's disease, malignancy, or hypertrophic arthritis, the last of which in particular, often causes pain in the right side simulating that due to a kidney stone or to a diseased gall bladder. The next step is to place the patient in the prone position and to take a series of gall bladder films with varying degrees of exposure. In the event of a suspicious shadow, a comparison of these films with the kidney films enables us to determine whether the calculus is anterior and hence probably a gall stone, or posterior and probably a kidney stone. The gall bladder films may disclose a long, palpable lobe of the liver, thus establishing the identity of a palpable tumor in the right upper quadrant.

From the survey of the first films we may determine the presence of an atrophic kidney, a large kidney, an irregular kidney, a polycystic kidney, a tuberculous kidney, a tumor of the kidney, a large hydronephrosis, or a ptosed right kidney. Further to confirm the diagnosis, catheterization of the ureters with X-ray catheters fol-

lowed by an X-ray examination will establish the cause of an ureteral obstruction, in case the catheter fails to pass up to the kidney pelvis, or it may disclose the presence of a double ureter. Suspicious shadows in the right side may appear to be in contact with the X-ray catheter. In such a case X-ray films should be taken with the patient in two positions in order to determine whether these shadows are from calcified glands or from some other source outside the ureter. These shadows may not appear to be in contact with the catheter in either position, or they may appear in contact in only one position. However, since occasionally shadows which appear to be at some distance from the catheter in both positions may nevertheless be stones in a redundant ureter or in a large dilated ureter, this examination should be followed by the injection of an opaque medium into the ureter and kidney pelvis to determine the size, shape and position of each. By this means an obstruction or a narrowing of the ureter from an ureteral calculus or a stricture may be seen; a bifurcation of the ureter may also be determined by this method.

After these two sets of films have been taken, the stomach is filled with a barium meal and observed fluoroscopically and by films to determine the presence of an ulcer or tumor, and also to discover the position and mobility of the stomach. As the barium passes into the duodenum, that also is examined to determine (1) its position; (2) the presence of an ulcer or of adhesions; and (3) the possibility of duodenal stasis, as disclosed by dilatation and retention. We have found that this last condition is often the cause of periodical headaches with vomiting of bile, and also of epigastric pain. Many patients who are suffering from duodenal stasis have undergone operations for suspected gall bladder disease without securing any relief from their symptoms. We now consider that a dilated duodenum is a distinct clinical entity; and we have found that in many instances relief from symptoms is secured by operation. This condition, therefore, should always be ruled out in cases of bilious headache, especially when there is a history of their occurrence over a period of several years.

Six hours after the examination of the duodenum another fluoroscopic examination is made and films are taken to determine whether or not there is any gastric retention. This examination may be of much importance in cases of carcinoma or of ulcer in particular, in indicating whether or not an operation should be performed. Even in advanced cases of carcinoma with retention a gastro-enterostomy should be done if sufficient stomach-wall is free from infiltration. Whether or not this is the case can usually be determined by the X-ray examination.

This opaque meal is followed through the intestinal tract and a barium enema is given on the following day to determine whether or not any pathological condition is present in the colon. Often this study discloses an abnormality in the position of the duodenum or colon in the right upper quadrant, thus indicating the presence of an extensive lesion which it is possible to identify as a carcinoma of the head of the pancreas.

Should the above consecutive examinations not indicate any pathological condition which accounts for the symptoms, then a gall bladder dye may be administered according to the plan outlined by Graham of St. Louis. This consists in giving the patient five capsules of one gram each of tetraiodo-phenolphthalein with the evening meal, each capsule being incorporated in a large capsule of soda. Gall bladder films are taken at 9 A. M., 1 P. M., and at 2 P. M. on the following day, after a meal rich in fats. If the gall bladder is normal it will be filled at 9 A. M., the shadow will be dense at 1 P. M., and the gall bladder will be almost empty at 2 P. M. on the following day. If it is not empty then, another X-ray film should be taken on the following morning. If no dye is seen in the gall bladder and the capsules have broken up in the intestinal tract, a diagnosis of gall bladder disease may be made. By this examination is is possible to determine whether or not the gall bladder is receiving bile, and if so how rapidly; and its emptying time can be determined. The dye also establishes the position of the gall bladder and may thus rule out an erroneous interpretation of a suspicious shadow which does not lie in this area. Moreover, a large stone in the gall bladder may show through the dye in the gall bladder as a shadow of definitely lesser density; and finally, the shape and location of the gall bladder may show whether or not there are adhesions to the duodenum.

Our findings in 418 cholecystograms may be summarized as follows:—

A pathological condition indicated in 240
No pathological condition indicated in.....171
Doubtful 7

Number of cases in which cholecystograms were followed by operation—26.

Comparison of cholecystographic and operative findings:—

(1) Cases in which cholecystograms showed no lesions but lesions were found at operation—3.

Stones 2
Cholecystitis 1

(2) Cases in which the indication of a pathological condition on the cholecystogram was confirmed at operation—21.

Stones 12
Chronic cholecystitis..... 4
Adenocarcinoma 2
Mucocele 2

No pathological report 2, but in these cases the gross findings at operation were: in one a fibrotic whitish gall bladder; and in the other a grayish gall bladder showing a moderate degree of inflammation.

(3) Cases in which the cholecystogram indicated the presence of a lesion but none was found at operation—2.

In these two cases the findings were as follows:—In one a soft, normal gall bladder, slightly fibrous wall; and in the other the colon was adherent to the edge of the liver, and the pathological report on the gall bladder was 'cholesterolosis'.

As shown above, in this series of 26 cholecystograms the findings were definitely confirmed at operation in all but 5 cases, or in 81 per cent.

Case 1-(116,015). The patient was a married woman, 23 years of age, who came to the Clinic because for two years she had had persistent pain in the right upper abdominal quadrant. This had been diagnosed as due to cholecystitis with stones, and three weeks before she came to the Clinic a cholecystotomy had been performed at which no stones or other pathological condition of the gall bladder had been found. The symptoms had been unrelieved.

An X-ray taken after the injection of sodium iodid showed dilatation of the right ureter above the stricture; and the diagnosis of hydronephrosis was made. Dilatation of the ureter relieved the symptoms.

In this case if a complete roentgenographical study of the right kidney and ureter as well as of the gall bladder region had been made when the patient first consulted a physician, she would have been spared an unnecessary operation.

Case 2-(114,047). The patient was a married woman, 38 years of age, who came to the Clinic because of persistent pain in the right side. This pain was characterized by severe spasms passing to the back and was associated with nausea and vomiting. She had had attacks of this kind during a period of about four years, the character of the pain and its intermittent nature giving rise to the suspicion that she had gall-stones, although there had been no jaundice or change in the color of the stools. On palpation of the right upper quadrant a tumor-mass was evident which was tender to pressure, and suggested an enlarged dilated gall bladder filled with stones.

An X-ray examination gave evidence of marked hydronephrosis of the right kidney; gall bladder plates, on the other hand, gave no evidence of any pathological condition.

The pyelogram confirmed the primary finding of hydronephrosis and a nephrectomy was performed at which the diagnosis was confirmed.

Such cases as these illustrate well some of the pitfalls which the physician and the roentgenologist alike must avoid in all cases in which the symptoms are referable to the right upper abdominal quadrant.

Effects of Sodium Tetraiodophenolphthalein On Some Vital Organs*

By C. K. Hsieh, M.D., *Peking, China*

THE remarkable Graham method for visualization of gall bladder since its discovery in 1923 (1) is now widely used as a routine procedure in the Roentgen diagnosis of gall bladder conditions. The high toxicity of the tetrahalogenophenolphthaleins employed in this test is well known as evidenced by the reports of some marked constitutional reactions after the administration of the drug sometimes observed in the earlier days of the development of this method of diagnosis. With the improvement of technique of administration and of purer preparation of the salts, however, any untoward effect has been eliminated. The substitution for the tetrabromphenolphthalein with the iodide which is about twice as heavy but has about the same toxicity, thus reducing the dosage to about one-half that of the brom-compound, further minimizes the unpleasant reactions (2). From the clinical standpoint, therefore, it seems this Roentgen visualization test with the sodium tetraiodophenolphthalein has been put on safe ground.

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However, pathological studies of the effects of these compounds have not been extensively done. The originator of the test, Graham, and his associates working with the usual diagnostic dosage of both the brom- and the iodosalts report that no pathological changes are found in the liver from both the dog and the human. (3) Ottenberg and Abramson (4) in determining the upper limits of the intravenous dosages of the tetrachlor- and tetrabrom- phenolphthaleins find extensive degeneration and necrosis of the liver of animals given doses of from 0.3 to 0.4 gm per kilo of body weight. Doses of from 0.4 to 0.5 gm per kilo kill rabbits at once and the livers are profoundly congested and microscopically there is acute degeneration of the liver cells. In his animals given doses from 0.1 to 0.2 gm per kilo there are no pathological changes in the liver or they are so little as to be considered negligible. These workers are of opinion that there is no gradation between the toxic and non-toxic doses. In the Pathological Laboratory of the University of Michigan Professor Warthin has found some fatty changes in some livers from human individuals after the use of the dye in the Graham test. It is the object of this study to determine whether

these fatty changes are of any significance or not, and also to observe its relationship to other pathological changes such as degeneration and necrosis.

PROCEDURE

In this experiment both the intravenous injection and the oral administration of the sodium tetraiodophenolphthalein were used. Thirty-four dogs were divided into two main groups: to one the intravenous injection was given and with the other the dye was administered by mouth. Each of the two groups was subdivided into two: one to determine the effects with increasing intervals of time and the other to observe the effects with increasing dosage. Livers from two cholecystectomized dogs of the surgical department of the University Hospital which were given the dye intravenously to study the bile passages were included in this series. Three normal dogs were used for control.

In Group I the dogs were given doses of 8 grains per 10 pounds in enteric-coated capsules by mouth (approximately 0.12 gm per kilo); and in Group III similar doses were used intravenously. These dogs were killed from within one day to two months. Doses ranging from 3.3 grains (human dose—5 gr per 15 lbs) to 40.0 grains per 10 pounds (about 0.05 to 0.58 gm per kilo) were given to animals of Group II by mouth and of Group IV intravenously; they were killed within one or two days if they survived.

All dogs given the dye orally were roentgenographed or fluoroscoped to note if any of the ingested capsules were undissolved. Some of those with the intravenous injections were also x-rayed for gall-bladder shadows. The animal dose (8 gr. per 10 lb) in most instances gave good shadows of the gall bladder.

In the intravenous injections 10 per cent solution of the dye was used and the injections were made in the femoral veins with the dogs under ether anesthesia. All dogs were killed with ether. These latter facts are of significance because the little histological changes found in cases given the small doses and in the controls can possibly be explained as the result of ether.

RESULTS

Controls: Findings of these normal dogs without the use of the dye are taken for control and the fat contents of the organs examined is considered as the standard.

NO.	LIVER	HEART
C-1 1660 LAD	Congestion + Fats + in liver cells and bile ducts	——
C-2 3355 LAD	Congestion + Fats + in liver cells Bile ducts—negative	——
C-3 3347 LAD	——	No fats

Group I (*Table* 1): Sodium tetraiodophenolphthalein in enteric-coated capsules was given by mouth in doses of 8 grains per 10 pounds. These dogs were kept from one day to two months. In the liver congestion of various degrees was found in those killed within one week. Slight amount of fat was present in the liver cells of

dogs killed within two weeks and in the bile ducts a small amount of fat was noted in all cases. The spleen showed little changes except congestion. Slight fatty changes were also present in the kidney in all except from 3.3 to 16.0 grains per 10 pounds by mouth there was some congestion but with no fatty changes in the liver. When the dose was raised to two or three times of the animal dose (i.e. 8 gr per 10 lb) in addition to the very

TABLE I

NO.	WT.	DOSE	X-RAY BEFORE OR AFTER DEATH	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS		
					LIVER	SPLEEN	KIDNEY
O-1 1164 LAD	48 lbs.	40 gr.	1 cap undis solved	17 hrs.	Congestion +++ (no fat stain)	Negative	Negative
O-2 1163 LAD	27 lbs.	20 gr.	None seen	17 hrs.	Congestion ++ (no fat stain)	Negative	Negative
O-11 1302 LAD	18 lbs.	15 gr.	None seen	18 hrs.	Congestion ++ Fats + Bile ducts—fats +	——	Congestion ++ Fats +
O-4 1339 LAD	40 lbs.	30 gr.	None seen	1 wk.	Congestion ++ (no fat stain)	Negative	Negative
O-5 1442 LAD	30 lbs.	25 gr.	None seen	2 wk.	Fats + in liver cells and	Negative	Fats +
O-6 1654 LAD	25 lbs.	20 gr.	None seen	1 mo.	bile ducts No fats Bile ducts—fats +	Negative	Fats +
O-7 2088 LAD	15 lbs.	10 gr.	None seen	2 mo.	Negative Bile ducts—fats +	Negative	Negative

Group 1—Dogs given sodium tetraiodophenolphthalein in capsules of 5 grains each in doses of 8 grains per 10 pounds by mouth and killed at intervals of from within one day to two months.

in the one killed at two months' interval. Congestion was the only prominent feature in the findings of this group; the slight amount of fat present in the liver cells and bile ducts seems to be compatible with the amount found in the control dogs.

Group 2 (*Table* 2): With doses of marked congestion there were considerable changes in the liver cells, disintegration of cells around the central veins (early necrosis) and very marked fatty degenerative infiltration both in the liver cells and the epithelium of the bile ducts. The spleen showed hemorrhages in some cases

TABLE II

NO.	WT.	DOSE	SYMPTOM	X-RAY BEFORE OR AFTER	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS			
						LIVER	SPLEEN	KIDNEY	HEART
O-8 1300 LAD	30 lbs.	10 gr. (man dose)	None	None seen	18 hrs.	Congestion + No fats	Negative	Negative	——
O-11 1302 LAD	18 lbs.	15 gr.	None	None seen	18 hrs.	Congestion ++ Fats + Bile ducts—fats +	——	Congestion ++ Fats +	——
O-9 1388 LAD	9 lbs.	15 gr.	None	None seen	24 hrs	Congestion ++ No fats	Congestion ++	Fats ++	
O-10 1390 LAD	16 lbs.	40 gr.	Very weak	None seen	24 hrs.	Congestion ++++ Early disintegration of central lobules	——	Congestion +++	——
						Fats +++ Bile ducts—fats+++			
O-13 1657 LAD	16 lbs.	40 gr.	Very weak	None seen	42 hrs.	Congestion ++++ Fats ++++ in liver cells; ++ in bile ducts. Slight degeneration of cells	——	Congestion +++ Fats ++	——
O-14 1658 LAD	16½ lbs.	55 gr.	Very weak and drowsy	3 caps undissolved	42 hrs.	Congestion ++++ Normal architecture Fats +++ in liver cells and bile ducts	Congestion +++ Slight degeneration	Congestion +++ Fats ++	——
O-15 3548 LAD	15 lbs.	50 gr.	Very weak and drowsy	None seen	24 hrs.	Congestion +++ Fats ++++ in liver cells and bile duct Marked degeneration (early necrosis)	Congestion +++ Slight degeneration	Congestion +++ No fats	Fatty degeneration ++
O-16 3549 LAD	13½ lbs.	45 gr.	Very weak and sick	None seen	24 hrs.	Congestion ++++ Fats ++++ in liver cells and bile ducts Early necrosis	Congestion +++ Slight degeneration	Congestion ++ Fats +	Fatty change ++++
O-17 3550 LAD	16 lbs.	40 gr.	Very weak and sick	None seen	24 hrs.	Congestion ++++ Slight disintegration of cells Fats ++++ in liver cells and bile ducts	Congestion ++ Slight degeneration	Congestion +++ Degeneration of tubules Fats++++	Fatty change ++++
O-18 3551 LAD	10 lbs.	40 gr.	Very weak and sick	None seen	24 hrs.	Congestion ++++ Early disintegration tion of cells Fats ++++ in liver cells and bile ducts	Congestion ++	Congestion +++ Slight degeneration Fats++++	Fatty change +

Group 2—Dogs given sodium tetraiodophenolphthalein in capsules of 5 grains each by mouth in doses from 5 grains to 40 grains per 10 pounds.

and degeneration of the cells, particularly those in the pulp. The kidney showed moderate congestion and fatty changes. The hearts of those dogs given the large doses presented degeneration of the myocardial cells with chloroform poisoning or poisoning with other toxic agents.

Group 3 (*Table* 3): Intravenous injections of the dye in doses of 8 grains per 10 pounds were given to the

TABLE III

NO.	WT.	DOSE	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS		
				LIVER	SPLEEN	KIDNEY
I-1 1160 LAD	65 lbs.	50 gr.	16½ hrs.	Congestion ++++ (no fat stain)	Congestion ++	Congestion ++
I-2 1196 LAD	23 lbs.	17 gr.	16 hrs.	Congestion ++ No fats	Negative	Congestion ++ Fats +
I-3 1338 LAD	25 lbs.	20 gr.	3 days	Congestion ++ (no fat stain)	Congestion +	Congestion +
I-4 1387 LAD	20 lbs.	16 gr.	1 wk.	Congestion +++ No fats	Negative	Fats ++
I-5 1443 LAD	25 lbs.	20 gr.	2 wk.	Congestion + No fats	Negative	Congestion ++ No fats ++
I-6 1655 LAD	10 lbs.	8 gr.	1 mo.	Congestion ++++ Fats + in liver cells and bile ducts	Congestion ++	Congestion ++ Fats ++
I-7 2089 LAD	45 lbs.	36 gr.	2 mo.	Negative	Negative	Chronic glomerulonephritis (apparently not related to action of the dye)

Group 3—Dogs given sodium tetraiodophenolphthalein in doses of 8 grains per 10 pounds intravenously and killed at intervals of from within one day to two months.

fatty degenerative infiltration. None of the dogs, however, succumbed, though they were all very weak and drowsy. The findings of this group, namely fatty degenerative infiltration and disintegration of cells of the liver, kidney, and heart suggest a similarity to those generally found in cases of animals of this group. There was congestion of different degrees noted in the liver, but no fatty changes, except in one dog which had been kept for one month. The kidney showed some amount of fat but this was not constant. The spleen showed practically no changes. The findings, on

TABLE IV

NO.	WT.	DOSE	SYMPTOM	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS			
					LIVER	SPLEEN	KIDNEY	HEART
I-8 1301 LAD	12	4 (man dose)	None	24 hrs.—killed	Congestion + Fats + in liver cells and none in bile ducts	Negative	Congestion + Fats ++	——
I-2 1196 LAD	23	17	None	16 hrs.—killed	Congestion ++ No fats	Negative	Congestion ++ Fats +	——
I-9 1389 LAD	35	56	Vomited Weak and sick	23 hrs.—killed	Congestion ++ Cells—Normal Fats ++ in cells and bile ducts	Congestion ++ Slight degeneration	Negative No fats	——
I-10 1391 LAD	38	92	Vomited Sick and weak Restless Rapid resp.	10 hrs.—died	Congestion ++++ Fats ++++ in cells and ++ in bile ducts Necrosis—central	Congestion +++ Slight degeneration	Congestion ++ Fats +++ Tubular cell cloudy	——
I-13 3230 LAD	19	46	Vomited Very weak Rapid and shallow resp.	4 hrs.—died	Congestion ++++ Early disintegration Fats ++ in cells and ++++ in bile ducts	Congestion ++++ Hemorrhage	Congestion ++ Slight degeneration of tubules Fats ++++	——
I-14 3365 LAD	11	26	Very weak and drowsy	7 hrs.—killed	Congestion ++ Early necrosis Fats +++ in cells and bile ducts	Congestion ++	Congestion ++ Cells—cloudy No fats	Degeneration of cells No fats
I-15 3353 LAD	18	43	Very weak and sick Rapid and shallow resp.	8 hrs.—died	Congestion ++++ Early necrosis Fats ++++ in cells and bile ducts	Congestion ++++ Degeneration Hemorrhage	Congestion +++ Desquamation of tubular cells Fats+	Degeneration of cells Fats++++

Group 4—Dogs given sodium tetraiodophenolphthalein in doses of 5 grains to 24 grains per 10 pounds intravenously.

the whole, are similar to those in *Group* 1.

Group 4 (*Table* 4): With increasing doses of the dye injected intravenously the changes were more evident and extensive than in cases of Group 2 in which the dye was used orally. Three of the four dogs given three times of the usual animal dose died in four to ten hours after the injection and the fourth one was killed seven hours after the injection. Disintegration of cells of the liver around the efferent veins with very marked congestion was noted in three. Extensive central necrosis of the liver was observed in the other that died in ten hours. This longer period of interval between the injection and death had probably provided sufficient time for the destructive process to go on to actual necrosis while in the other three cases the changes were not completed. Marked fatty degenerative infiltration was found in all these cases and seemed to precede the necrotic changes. In the kidney, congestion, moderate fatty changes and cloudy swelling, with even desquamation of the cells of the tubules were noted in cases given the high dosage. The spleen showed considerable congestion and even hemorrhages in some cases and degeneration of cells. The heart in two dogs examined showed marked degeneration in both, and marked fatty degeneration in the one that died. The cause of death of these dogs was apparently myocardial weakness and failure.

TABLE V

NO.	WT. IN LBS.	DOSE IN GRS.	INTERVAL BETWEEN INJECTION AND DEATH	PATHOLOGICAL FINDINGS OF LIVER
I-11 1656 LAD	32	25	8 hrs.	Congestion ++ Fats ++ in liver and bile ducts
I-12 1788 LAD	35	28	8 hrs.	Congestion ++ Fats ++ in liver cells and bile ducts

Group 5—Dogs cholecystectomized six months previous to intravenous injections of sodium tetraiodophenolphthalein in doses of 8 grains per 10 pounds.

Group 5 (*Table* 5): These two dogs had been cholecystectomized about six months before the intravenous injections of tetraiodophenolphthalein; the dose was the usual one for dogs as used in Groups I and III. The pathological findings were essentially the same as in those in Groups I and III. The absence of the gall bladder had in no way increased or decreased the effect of the dye on the liver.

SUMMARY

1. The effects of sodium tetraiodophenolphthalein on some vital organs were studied as regard changes in time and in increasing dosage. Thirty-one dogs were given the dye either orally or intravenously and three dogs were taken as controls.

2. Either orally or intravenously small doses of from 3.3 to 16.0 grains per 10 pounds gave only congestion with but little fatty changes in some cases and these changes were so minimal that they could be considered to be within normal limits. Therefore it is safe to conclude that the ordinary human dose of sodium tetraiodophenolphthalein as used in the Graham test is under the toxic limit.

3. With the larger doses marked degenerative changes were observed in the liver, spleen, kidney, and heart; fatty degenerative infiltration was the most conspicuous finding in all cases and this seemed to be the forerunning change of actual necrosis. Extensive necrosis was present in one case. In view of these very marked toxic effects with over dosage, therefore, great caution should be taken in the administration of this iodo- or similar compounds.

4. With small doses both oral and intravenous methods of administration of the dye are safe and their effects on the body tissues are apparently about the same in degree. But with over doses intravenous injection of the dye produces much more extensive damage and in shorter time. So in using the intravenous method still greater care should be taken.

REFERENCES

(1) GRAHAM, E. A., AND COLE, W. H.: Roentgenological examination of the gall bladder; preliminary report of a new method utilizing the intravenous injection of tetrabromphenolphthalein. J. Am. M. Ass., Feb. 23, 1924, lxxxii, 613.

(2) WHITAKER, L. R., AND MILLIKEN, G.: A comparison of sodium tetrabromphenolphthalein with sodium tetraiodophenolphthalein in gall bladder radiography. Surg., Gynec. and Obst., Jan., 1925, xl, 17.

(3) GRAHAM, E. A., COLE, W. H., AND COPHER, G. H.: Cholecystography: its development and application. Am. J. Roentgenol. and Rad. Therapy, December, 1925, xiv, 487.

(4) OTTENBERG, R., AND ABRAMSON, H. A.: Production of liver necrosis by tetrachlorphenolphthalein and tetrabromphenolphthalein. J. Am. M. Ass., March 14, 1925, lxxxiv, 800.

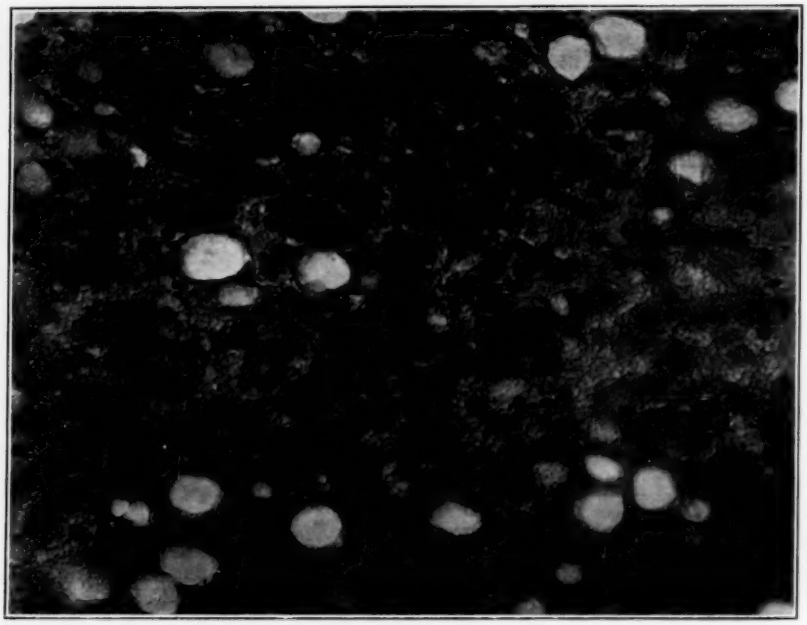

FIG. 1—Liver from animal O-14 given 4X animal dose orally. Marked congestion and diffuse fatty degeneration. Early necrosis in central portions of lobules. Older fatty infiltration.

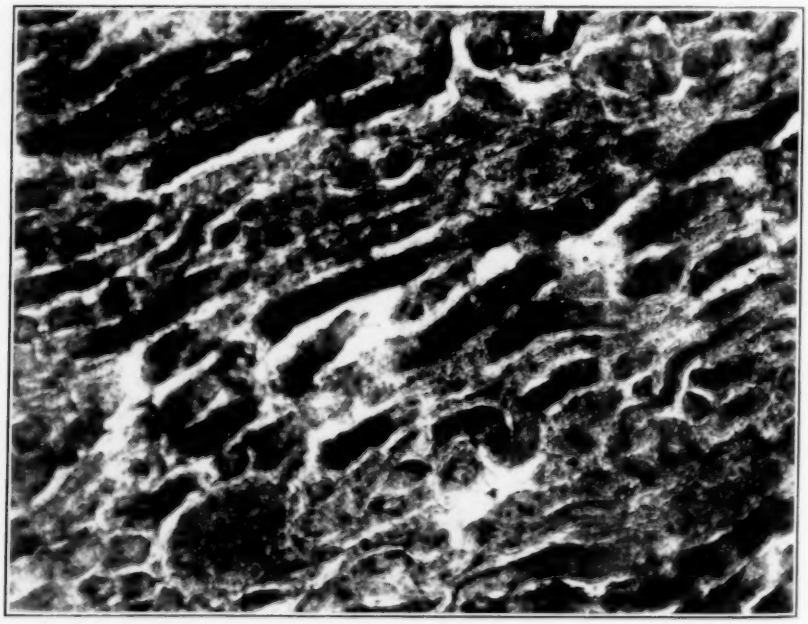

FIG. 2—Kidney from O-14 (4X animal dose orally). Marked congestion and lipoidosis, particularly of collecting tubules in medullary rays of cortex. Sudan III stain. Dark tubules show extreme lipoidosis.

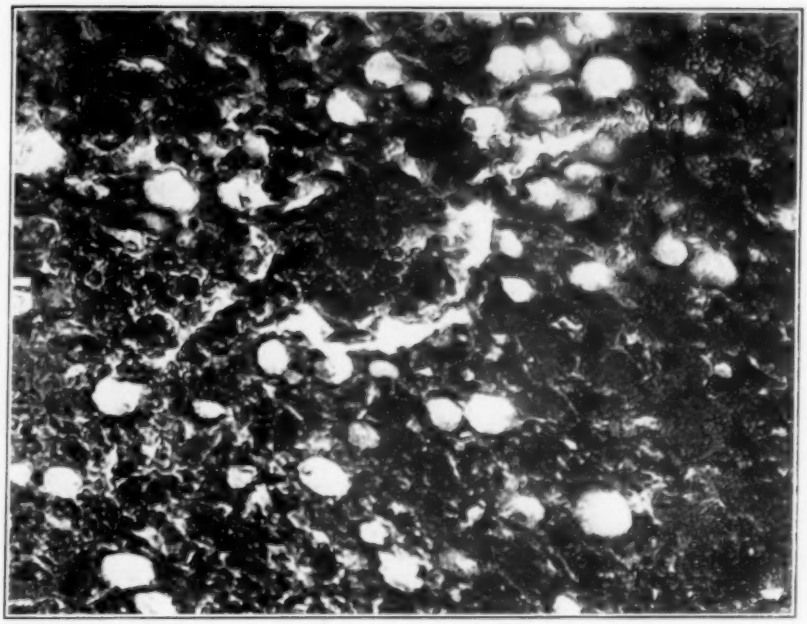

FIG. 3—Animal O-10. (3X animal dose given orally). Marked congestion, fatty degenerative infiltration and fatty infiltration of liver, with marked cloudy swelling and beginning necrosis of liver cells.

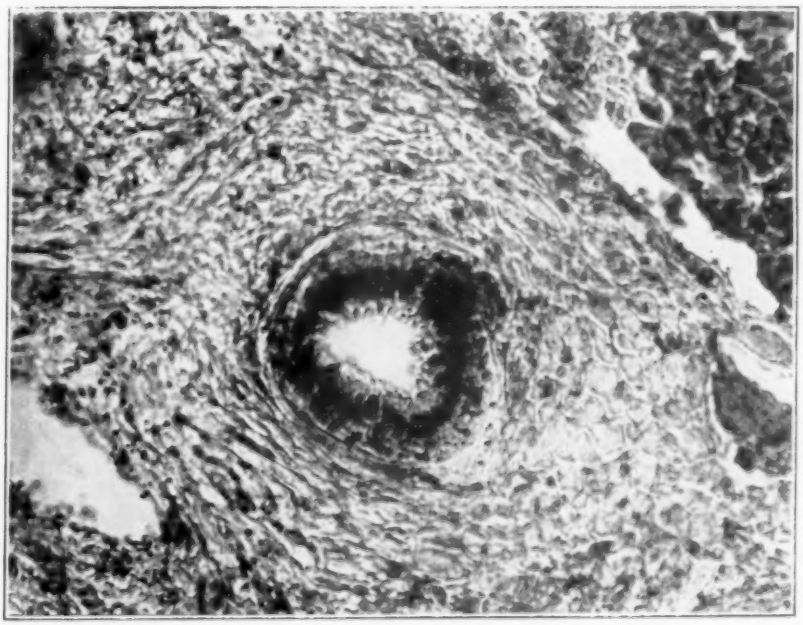

FIG. 4—Bile duct from liver of preceding, showing the marked lipodosis of epithelium. Sudan III stain.

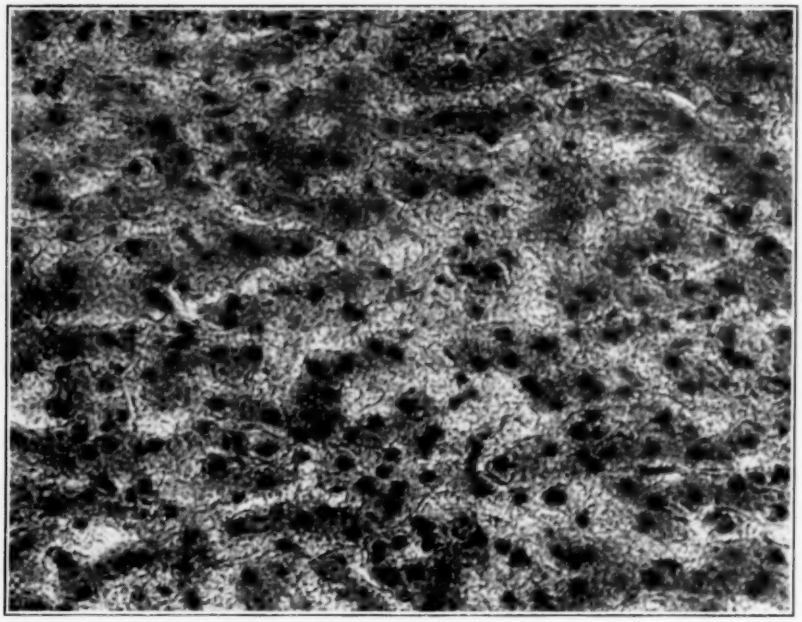

FIG. 5—Dog I-15. (3X animal dose intravenously; died). Liver showed marked congestion diffuse fatty degenerative infiltration and marked lipoidosis of bile ducts. Disintegration of liver cell nuclei.

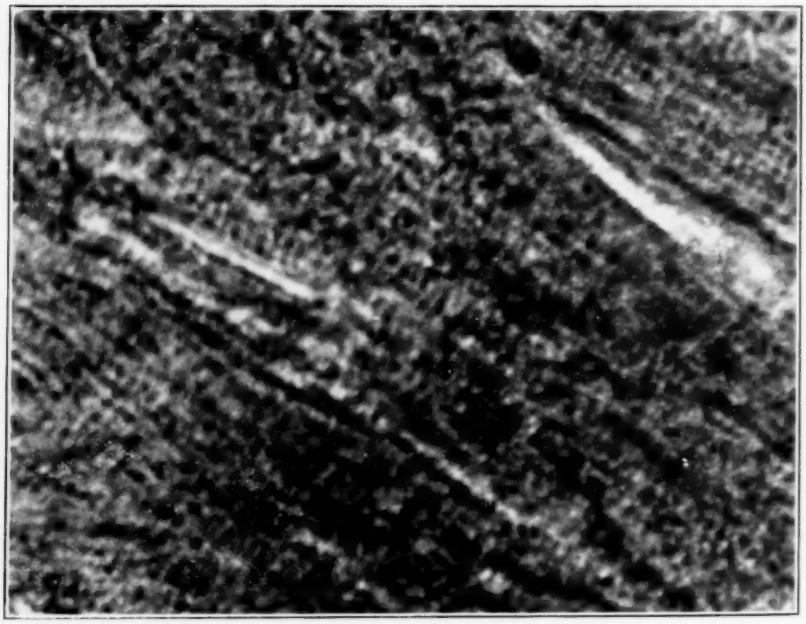

FIG. 6—Heart of animal in preceding figure, showing diffuse fatty degenerative infiltration and cloudy swelling. High power view of muscle fibers.

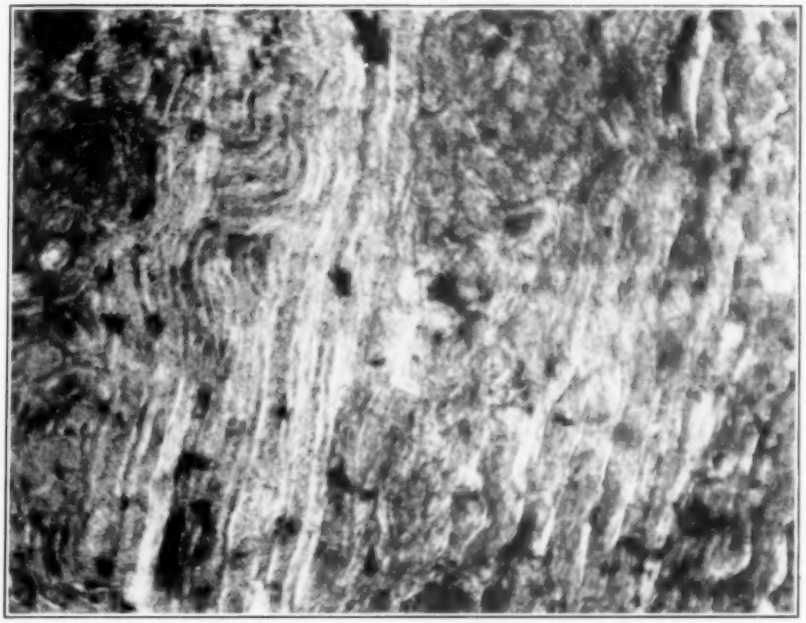

FIG. 7—Kidney from dog I-11 (Cholecystectomized. Usual dose given intravenously.) Kidney and liver showed marked congestion and lipoidosis. Sudan III stain.

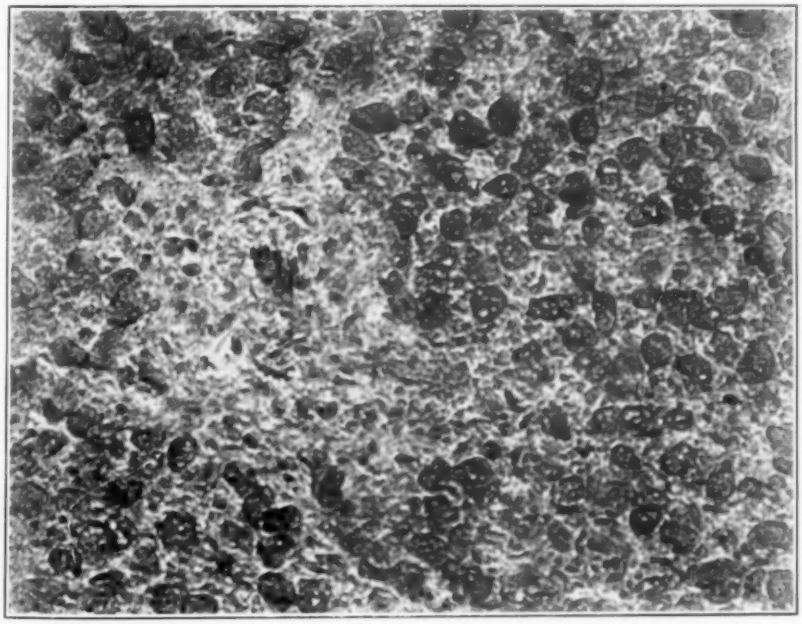

FIG. 8—Dog, I-10. (3X animal dose intravenously, causing death.) Liver showed advanced cloudy swelling and necrosis of central portions of lobules, marked congestion, diffuse fatty degeneration, and marked lipoidosis of bile-ducts.

Further Observations in Cholecystography So-called Danger in the Use of Tetraiodophenolphthalein*

By Maurice Feldman, M.D., *Associate in Gastro-Enterology, University of Maryland, Baltimore*

SINCE the advent of cholecystography numerous communications have appeared directing attention to the toxicity, as well as to the hepatic and renal lesions which have been attributed to the dye, (tetraiodophenolphthalein) utilized in visualizing the gall bladder. Graham and Cole, (1) as well as Ottenburg and Abramson, (2) were able to produce lesions in the liver and kidneys following injections of large amounts of the dye intravenously in animals. Rosenau (3) also points to the clinical and experimental work as indicating the possibility of liver damage following these injections, and cautions that these forms of dyes should be employed cautiously and only in moderate doses.

In as much as the oral method of gall bladder visualization is nowadays practiced to a large extent, replacing the intravenous method, it appeared important to us to determine whether a similar toxic effect or liver damage might also arise as the result of this method of administration. From numerous experiments performed by Friedenwald, Kearney and myself (4) on animals following the oral administration of the dye, even when given in massive doses, it was observed that neither degenerative nor necrotic changes could be produced in the liver or kidneys.

In order to determine, however, whether pathological changes are produced in the human subject as an effect of the dye when given orally for purpose of cholecystography, an attempt was made to correlate certain clinical symptoms in a large series of cases following its employment.

On this account the following questionaire was sent to twelve prominent radiological clinics.

State the approximate number of cases upon whom the gall bladder visualization test has been made.

In your experience, could death of any patient be attributed directly to the tetraiodophenolphthalein dye? If so, state number of cases and whether the dye was administered by the oral or intravenous method.

In your experience has the dye produced extreme toxic symptoms followed by inflammatory changes in the liver (hepatitis)?

State number of cases in which

*From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland.

jaundice followed the administration of the dye.

State the cause of jaundice.

The results were as follows:

Total number of cases collected	18,000
Death attributed directly to the tetraiodophenolphthalein	none
Extreme toxic symptoms (Signs of hepatitis)	none
Jaundice following the administration of the dye	3

Jaundice existed previous to the adtion of the dye in one of my cases. This was caused by a stone in the common duct producing obstruction. In only two other instances of the 18,000 cases was jaundice noted following the use of the dye. In these cases a stone in the common duct was also observed at operation.

In many instances in our series jaundice existed previous to the administration of the dye, which was in no way intensified by the dye. A similar observation has been noted by others.

CONCLUSIONS

As the result of a collective investigation of 18,000 cases in which cholecystography was performed, the dye being administered by the oral route, the results uniformly indicate that this method is free from all danger; furthermore, there has been no evidence presented to indicate that any degenerative changes have been produced in the liver or kidneys by this procedure. The conclusions have been fully confirmed by the experimental findings on animals, already reported by Friedenwald, Kearney and myself (5).

REFERENCES

(1) Graham and Cole: Jour. A. M. A. 82, 163 (Feb. 23) 1924.

(2) Ottenburg and Abramson: Jour. A. M. A. 84, 800 (Mch. 14) 1925.

(3) Rosenau: Jour. A. M. A. 85, 2017 (Dec. 26) 1925.

(5) Friedenwald, Feldman and Kearney: Radiology, 9-Nol, 68, (July) 1927.

(5) Friedenwald, Feldman and Kearney: Jour. A. M. A. 89, 195, (July 16) 1927.

Editorials

BENIGN GLYCOSURIA

IT is usually the general practitioner who makes the discovery that a given individual has glycosuria, and such discovery is generally based upon a more or less crude use of the Fehling's test. If any reduction takes place, be it rapid or slow, slight or marked in degree, the decision is quickly made that glycosuria is present and the individual a diabetic. The physician is very likely to forget that other substances, conjugated glycuronic acid, alkapton, lactose, pentose, and excessive amount of uric acid or creatinin, may reduce alkaline copper sulphate solutions. He usually does not control the reduction by the application of other tests, and all too frequently he is not in a position to make a blood sugar examination. In the first place he is unable to tell whether glycosuria is actually present or not, and in the second place, should it be really present, he cannot tell whether the individual has true diabetes or a benign glycosuria. Of the latter possibility it is quite likely he has never heard. The unfortunate Fehling's-reducing patient, therefore, is labelled diabetic, and his life henceforth becomes an existence of care, anxiety and denial, and of all the unpleasant features that attend living on a diet. Or worse, insulin treatment may be instituted at once, with unfortunate results. If an applicant for life insurance, his application may be rejected. The consequences of such errors in diagnosis may, therefore, be very serious, not only from a physical and psychical standpoint, but also as regards social and economic considerations. Yet it can hardly be doubted that in most communities there are individuals in this very situation of living as diabetics when they have no diabetes. In the first place it should be emphasized that non-diabetic glycosuria is of very frequent occurrence. Faber has stated that in an ordinary medical department the examination of the urine from all of the patients who have partaken of a meal containing much sugar will show glucose to be present in the specimens of urine in from 20-30 per cent of the patients. After an alimentary ingestion of larger quantities of glucose considerable glycosuria may be seen in 33 per cent, and even after the ingestion of starch glycosuria will occur in about 20 per cent. Holst made a study of 163 individuals rejected by life insurance companies as diabetics because of glycosuria and found that only 30 per cent were true diabetics; the remainder had benign glycosuria. When twenty-seven cases of the latter were studied over periods of from one to twenty-five years no other sign of diabetes developed, although the majority had given up any diet. By repeated examinations of the same patient he has demonstrated that year by year the administration of 50 gm. of glucose would give a blood

sugar rise to about 0.20 per cent, the patient showing constantly a harmless cyclic glycosuria. It may be difficult to distinguish between these cases and an early diabetes when the cyclic glycosuria is not due to a low threshold. Holst calls attention to the fact that when a patient lives on full normal diet without carbohydrate restrictions, an absolutely normal fasting blood sugar will almost with certainty rule out true diabetes. Should a cyclic glycosuria set in during the course of the day, it is due either to too low a threshold or to too great an alimentary rise, without in either cases denoting an abnormal metabolism, or having any serious influence on the future of the individual. Extensive studies of the glycosuric threshold, both in diabetics and in non-diabetics, carried out by Faber and others have shown that the glycosuric threshold varies in different individuals, but has a fairly constant position in the same individual. In the diabetic this position is independent of the duration of the disease or of the age of the patient. In normal individuals a low glycosuric threshold is simply an individual constitutional peculiarity, and, as far as he is concerned, is harmless. Such facts must be recognized by practitioners, and especially by those who examine for life insurance. The practical importance of a knowledge of benign glycosuria is very great for the individual concerned, and he must be protected from the dangers of an erroneus diagnosis of diabetes. Insignificant transient glycosurias must not be interpreted as diabetes. While the sugar threshold of a given individual is to be regarded as an inherent constitutional quality of the individual, and varying considerably in different individuals, it may change under varying conditions. Thus an experimental glycosuria without hyperglycemia may be produced by the administration of phloridzin and a few other substances. Pregnancy is also a factor that influences the position of the threshold. Through numerous investigations it is now well known that glycosuria with normal blood sugar is not infrequent in Pregnancy. It has even been proposed to use this symptom as a diagnostic factor of early pregnancy. Its value in this respect is but little, since it is not a constant phenomenon in the pregnant, and may occur in the non-pregnant. Nevertheless, it is in itself a significant phenomenon in the light it throws upon the problem of the glycosuric threshold. Studies by Faber have shown that in some normal pregnant women the threshold may fall throughout pregnancy on a normal diet. The patients were usually sugar free in the mornings. The normal threshold was not reached until several weeks after parturition. Abnormal conditions in the blood sugar threshold, constitutional or due to changed conditions as pregnancy, may thus give rise to glycosuria without hyperglycemia, and such glycosurias may be permanent or transient. Some individuals are born to be glycosurics and show this phenomenon throughout life, just as others are born to alkaptonuria, pentosuria or some other peculiarity of metabolism. These peculiarities of the sugar-regulating apparatus are abnormalities of the constitution, but they do not constitute diabetes. Their lives may proceed regularly enough and comfortably enough if their peculiarity

is not discovered by some practitioner or examiner who labels it diabetes. Numerous cases of this kind have been studied for long periods, and the low glycosuric threshold has not been shown to exert any influence either upon the course or the duration of life. Inasmuch as diabetes is one of the best advertised diseases of man and has come into the mental limelight of the layman, the testing of urine for glucose is more and more frequently asked for and made. Glycosuria is, therefore, more and more frequently discovered, and incorrect interpretations of benign glycosuria as diabetes are correspondingly more frequent. It is increasingly important to insist that the diagnosis of diabetes cannot be based upon the symptom of glycosuria alone, but that accurate determinations of the fasting blood sugar must determine the diagnosis. This is just as important for the diabetic as for the non-diabetic. Inasmuch as the diabetic in many cases has no other clinical symptom than the glycosuria the fasting blood sugar determination is as necessary to his diagnosis as the negative results of this determination are to the non-diabetic. Mistakes in either direction are disastrous. If the fasting blood sugar is abnormally high the diagnosis of true diabetes should be made. When there is a normal fasting blood sugar, a number of determinations should be made at intervals of several weeks. In the meantime the patient should continue his regular diet with carbohydrates. If the patient for a long time has shown a normal fasting blood sugar, that is below 0.11 per cent, it is highly probable that the glycosuria is of benign character and not a sign of diabetes. The determination of the type of glycosuria may then be carried out by determining several curves after the administration of carbohydrates. When a low threshold is found to be the only cause of the glycosuria, the latter may with certainty be regarded as benign. The problem is more difficult in the case of an alimentary rise of abnormal height. Benign glycosuria may be the result of an inherent deficient blood sugar regulation, and due either to an intrinsic low threshold or to an abnormally high alimentary blood sugar rise. In some individuals both conditions may occur, but more frequently a benign glycosuria is dependent upon too low a threshold. In 75 cases of benign glycosuria studied by Holst a low threshold was found in 22, an abnormally high rise in blood sugar in 15, and a combination of low threshold and high alimentary rise in 11; in 27 cases the type was not determined. Holst and Faber declare that in both cases, low threshold or high alimentary rise in blood sugar, it is a matter of individual peculiarity rather than of metabolic disease; and that in their experience they have never known a case which at first was definitely determined as benign to turn out to be a true diabetes. A cyclic alimentary rise may be present for years without ever changing into diabetes. It is, therefore, extremely important to the patient to have a correct differentiation made as to the nature of any existing glycosuria. Undoubtedly there are throughout the county great numbers of individuals with benign glycosuria who have been incorrectly diagnosed as diabetics, who have been refused life insurance, who have unfortunately been subjected to

the dangers of insulin treatment, or to rigorous and unnecessary systems of diets; and all of them suffering more or less from the psychical, social and economic results of the incorrect interpretation. In spite of the diagnosis and treatment they live on for years without showing any other evidences of diabetes. Would they not have been infinitely better off if at the beginning the glycosuria had been interpreted as a benign individual peculiarity and not as diabetes? Faber's Clinical Lecture* upon this subject should be read by every practitioner.

APOLOGY FOR DELAYED JOURNAL

The delay in getting out the summer numbers of the Annals of Internal Medicine has been due to various conditions attending the change of publishers from a commercial firm to the College. Various legal questions had to be settled, and the last number of the last volume, the June number, had to appear before the new volume could be begun. Difficulties are now apparently over, and all perplexing problems met by legal advice, so that the numbers should now appear without further delay. The September and October numbers are on the press and will be shortly sent out; the November number is out in galley proof, and by the first of the year the Annals of Internal Medicine should be on a regular schedule. The increase in subscribers for the new volume has been so great that the July number has been exhausted, and it has been found advisable to print 300 more copies. This fact in itself is very gratifying to the College.

*Lectures on Internal Medicine, Knud Faber, Paul B. Hoeber, New York, 1927.

Abstracts

Dynamics of Histogenesis in Cardiac Repair. The Role Played by Connective Tissue. ORMAN C. PERKINS and ADAM M. MILLER (Archives of Pathology, May, 1927, page 785).

These writers have studied the elastic tissue of the heart wall at different ages. They find that with increasing age, without other cardiac or other vascular lesions, there is an increase in the amount of elastic tissue in the different layers of the heart wall. In cases of arteriosclerosis in which the heart wall is damaged as the result of nutritional disturbances, the connective tissue of the epicardium, myocardium and endocardium increases in amount, the increase being characterized by the appearance of large quantities of elastic tissue. The amount of elastic tissue appears to be directly proportional to the damage suffered by the cardiac muscle. In toxic conditions with sudden effect on the heart, formation of elastic tissue does not occur in conjunction with the damage to the heart muscle, but in toxic conditions in which the attack on the heart is prolonged a marked development of elastic tissue takes place. The elastic tissue may be regarded as a compensatory mechanism in the heart wall when there has been slow damage to the cardiac muscle. They conclude from the evidence afforded by their material that collagenous fibers may be transformed into elastic tissue in consequence of prolonged stress and strain on the connective tissues containing the collagenous elements. The elastic fibers are derived directly from collagenous fibers which are so situated that they are subjected to an active existence rather than a passive one.

On Bile Stimulation of Pancreatic Secretion. A. C. IVY and H. C. LUETH (Proc. Soc. for Exper. Biol. and Med., June, 1927, page 837.)

Mellanby found that the injection of bile of an adequate reaction into the duodenum of the cat stimulates the pancreas, and that this was the case after ligation of the pylorus and bile ducts, and after atropine and ergotamine. He suggested that bile is the intestinal stimulus of pancreatic secretion, functioning by causing the elaboration and absorption of secretin. However, in his experiments bile may have caused stimulation by a local nervous mechanism that is not acted on by atropine or ergotamine. The present work was done on dogs. The investigators found that bile by stomach tube stimulates pancreatic secretion, but not invariably and to the extent that N/10 HCl does. Bile applied to the Thiry fistula of a pancreatic-transplant-Thiry-fistula preparation, stimulates the transplant occasionally, but not uniformly. Bile applied to a pan-

creatic-transplant - jejunal - transplant, preparation does not stimulate, whereas N/10 and N/20 HCl do. The authors, therefore, conclude that bile stimulates pancreatic secretion, but is not as potent as N/20 HCl; and that bile is an adjuvant, but not an essential alimentary stimulus of pancreatic secretion in the dog.

Scarlatinal Nephritis Experimentally Induced in the Dog. CHARLES W. DUVAL and R. J. HIBBARD (Proc. Soc. for Exper. Biol. and Med., June, 1927, page 876).

According to these workers the dog is not only highly susceptible to infection with *Streptococcus scarlatinae* but will develop regularly a severe and often fatal form of acute glomerulonephritis following the injection of the specific streptococcal toxin alone. The animals show no exanthem, but the lesions are regarded as corresponding histopathologically to the glomerular and acute interstitial scarlatinal nephritis of man. Eight young healthy dogs were injected with 5 mils each of filtered streptococcal "lysate" which had been prepared *in vivo* after the method previously described by the authors. Within 4-6 hours they developed symptoms of toxemia, and 24 hours later were extremely ill. The urine microscopically was bloody, and analysis showed quantities of albumin, granular casts, bile and blood. Two of the animals died on the fourth and 3 on the fifth day following the inoculation. The others survived, and though apparently well have continued to show, at intervals, albumin and casts in the urine. Sacrificed two months later, these animals showed varying degrees of chronic diffuse nephritis. The lesions of experimentally produced nephritis with *Streptococcus scarlatinae* may be primarly glomerular or interstitial, the determining factor depending upon the character of the material employed. The glomeruli are first affected when the toxic principle alone is used, regardless of whether the injection is made intravenously or subcutaneously. On the other hand the primary interstitial form occurs in the animals inoculated with the living culture, and in which a generalized infection has resulted. The acute interstitial lesion is a focal infiltration of the intertubular tissues with cells of the lymphocytic variety. As a rule neutrophiles are absent or few in number; in more advanced lesions they occur, but are not as numerous as the lymphoid and plasma cells. Associated with the interstitial lesions are viable streptococci which are readily demonstrable in stained sections, and recoverable in pure culture from the fresh tissue. The absence of fibroblasts or any other evidence of stromal activity in the early interstitial lesion is of significance. This fact would indicate that the lymphocytic infiltration is a true reaction on the part of the host to the injurious agent and in no sense reparative. From this it may be inferred that acute interstitial scarlatinal nephritis of man is the same kind of reaction. In regard to the primary glomerular lesion in the dog, the streptococcus toxin affects especially the capillaries of the kidney tufts, producing various alterations in the whole glomerular structure. There are lesions in the wall of the capillaries which cause the formation of thrombi, in consequence

of which the vascular loops become greatly dilated, occluded and later adherent to Bowman's capsule. Other glomerular tufts become enlarged through the appearance of numerous endothelial cells in the lumina of the capillaries. Bowman's capsular spaces generally contain blood in the form of hyaline masses, also albuminous material and desquamating epithelium, Later, in the capsular spaces where hemorrhage has occurred, early epithelial proliferations ("crescent" formation) are noted. All these structural changes cause the glomeruli to undergo further and more serious alterations through replacement by fibrous connective tissue of the destroyed capillary loops. While tubular changes are not an early feature in either the glomerular or interstitial type of experimental scarlatinal nephritis, they occur later in the process and appear in the form of epithelial degeneration, especially of the convoluted portion of the tubules. The living cells become swollen through the presence of fluid, granules, fat and hyaline droplets. Often the lumen is filled with blood, desquamated epithelium, granular and hyaline casts. Macroscopically the acute lesions of experimental nephritis in the dog are recognized by increase in the size of the kidney, swelling of the glomeruli so that they project above the cut surface, and by pinhead and smaller discrete yellowish white foci in the cortical substance and by scattered hemorrhages throughout the parenchyma. The investigators conclude that the various types of glomerular and acute interstitial nephritis of human scarlet fever can be regularly produced in the dog with the culture and with the pure toxic principle of *Streptococcus scarlatinae,* and that these experimentally produced nephritic lesions are alike in kind and variety to the acute scarlatinal nephritis of man. The complete analogy affords the opportunity of study of the acute lesions in their related sequence. Unfortunately the photomicrographs accompanying this preliminary report are very poor and far from convincing.

Ein Beitrag Zur Frage der Milzh ämolyse. E. Lauda (Zeitschr.. f. d. ges. exper. Med., Mai, 1927, s. 505). The hemolytic function of the spleen has been almost universally accepted, and this organ has been generally regarded as the seat of normal hemolysis for worn-out red blood cells, and also for pathological forms of excessive hemolysis. Many observations on splenic pathology, and especially the therapeutic results obtained by different workers through splenectomy in hemolytic icterus, have spoken in favor of an active splenic hemolysis. The present day teaching that this red blood cell destroying function of the spleen is manifested both as a normal function and under pathological conditions is based upon numerous pathological observations and animal experiments. Under a variety of conditions phagocytosis of red cells and deposits of iron-containing pigment occurs in the spleen; nevertheless, neither of these two facts can be taken as positive proof of an *active hemolytic* function of the spleen. If the spleen does possess an active hemolytic function there should follow, after its removal, an increase in the number of red cells. The results of experimental work in

this direction vary greatly; some authors have found after splenectomy at least a temporary increase in the red cells; others have had contradictory results. These experiments can hardly be regarded as conclusive. Of greater significance is the finding, reported by numerous observers, that red cell resistance is increased, at least temporarily, after splenectomy. Studies of the splenic vein blood, with reference to the problem of an active hemolytic function on the part of the spleen have produced results so divergent that they have not contributed decisively to the settling of the problem. Lauda has produced a new research aiming at its solution along the following lines: comparison of red cell counts in the splenic vein and in other regional veins; changes in morphology of red cells in splenic vein; differences in resistance of red cells from splenic vein and those from other parts of the body; and the bilirubin content of splenic vein blood. As a result of his investigations he concludes: 1. Exact determinations of the red cell count in the splenic vein of dogs are attended by insurmountable difficulties. Comparative determinations of red cells in splenic vein and splenic artery, and in veins of other regions offer no evidence in favor of an active hemolytic function on the part of the spleen. 2. The observations of Heeres and Buschen that morphological abnormalities occur in the red cells of the splenic vein could not be confirmed. 3. No differences in the resistance of the red cells in the splenic vein and those of other veins either in the normal or the toluylenediamine-poisoned dog could be demonstrated. 4. The splenic vein blood, neither in the normal animal nor in the toluylenediamine dog, showed any increase in bilirubin values over blood from other regions of the body. Lauda's results are, therefore, contradictory to those of many other observers. They show, at least, that the question of an *active* hemolytic function of the spleen is still an open question, insofar as experiments based upon the examination of splenic vein blood with respect to number, morphology and resistance of erythrocytes and bilirubin content are concerned.

Versuche über Inhalation von Insulin. Arnold Palm (Zeitschr. f. d. gesam. exper. Med., Mai, 1927, s. 432). Since it had been suggested that insulin inhalation might be used to avoid injections, Palm made a thorough study of various spray methods of administering insulin, and came to the conclusion that there was no chance of its becoming a practical method. In the watery solution necessary for use as a spray insulin was largely or wholly destroyed, so that excessive quantities would have to be used in order to obtain an effective dose. The method is, therefore, costly and wasteful.

Reviews

Clinical Case Taking. Supplement to Methods in Medicine. By GEORGE R. HERRMANN, M.D., Ph.D., Assistant Professor of Medicine, Tulane University, New Orleans. 90 pages. C. V. Mosby Company, St. Louis, 1927. Price in cloth, $1.50.

This manual of case-taking is offered as a supplement to the author's Methods in Medicine, the Manual of the Medical Service of George Dock, published in 1924. It consists of diagnostic data arranged as logically as possible in the natural sequence of the history, physical and laboratory examination. The introductory paragraphs emphasize the value of complete case records and outline the general principles involved in their preparation and the most important points in the technique of case-taking. The necessary administrative data are given as a front page to the record. The circumstances and condition at entrance are then to be described. Following this the present illness is considered, and the special points to be emphasized in regard to the chief complaint are outlined. The more common conditions to be considered under each of the common symptoms are given in detail; and the special points to be emphasized when the present illness suggests system disease are shown. The system review is followed by the social history, past history, family and marital history; and the essential features to be stressed in each type of case are given. The physical examination is next outlined in detail; and items of especial importance in various types of cases indicated either by parentheses or especial paragraphs. The laboratory examinations are simply mentioned and references given to complete descriptions of the same in Methods in Medicine. The minimum total requirements for the various types of cases, including the desirable routine laboratory studies, are indicated. Directions are then given as to tentative diagnoses and for further procedures that may be necessary in the handling of the patient. An Appendix contains outline figures showing the different habitus groups, outlines of organs, surface landmarks, region outlines, skin and segmental distribution. This manual of case-taking represents the highest ideals in the teaching of medicine, the inspiring of the student to the scientific attitude of mind, the honest complete study of the patient from all possible sides in the solution of the problem of his ailment. Only by such detailed and thorough methods of clinical approach can medicine be saved from the failures of ignorance and incomplete examination or from the slough of dishonest quackery. The student of character and mentality will comprehend the importance of such thorough and methodical examinations and will endeavor to become master of the details involved in a complete examination of a patient; the poor and lazy student will complain that such detailed outlines are beyond his time and ability, and are, therefore, idealistic and not practical. The author has answered this latter argument in his preface. We recommend this manual of case-taking to every medical student who wishes to get the best out of his medical training, and to be able to approach that great unknown, the patient's disease, with the confidence that only the knowing how to do it can give him.

History of Cardiology. By LOUIS FAUGERES BISHOP, M.A., M.D., Sc.D., F.A.C.P. Formerly Professor of Diseases of the Heart, Fordham Medical School, New York City. Consultant in Diseases of the Heart, Lincoln Hospital, New York; and JOHN NEILSON, JR., B.S., M.D., Assistant in the Cardiac Clinic, St. Luke's Hospital, New York. With an Introduction by

Victor Robinson, Ph.C., M.D. 71 pages. 12 Portrait illustrations. Medical Life Press, New York, 1927. Price in cloth, $5.00.

This interesting monograph on the history of cardiology sketches the development of our knowledge of the heart through three periods classed by the authors as the Pre-Scientific period, the Period of Scientific Investigation and the Period of Scientific Application. During the first of these periods the knowledge of the circulation and its disorders was very obscure, and circulatory phenomena were regarded with superstition or awe. Only a few of the ancient thinkers sought for some explanation of the beating of the heart, the pulse and other circulatory manifestations. Plato, while considering the heart in a more or less philosophical sense, vaguely hinted that the heart was the ruler of the arterial circulation. Aristotle believed the heart to be the source of the blood and that the blood in turn was the general nutritive fluid of the body. He thought that the beating of the heart and the pulsation of the vessels were due to the expansion of the blood within these cavities rather than to any active motion of the fluid itself. He did not consider the pulmonary arteries and veins as part of the circulatory system, but believed them to be wholly separate. He observed that the heart contained blood and not air, as was a common belief of the period. Praxagoras (300-400 B.C.) was the first to make a clear distinction between arteries and veins. He thought that the arteries contained no blood but a mysterious vapor; only the veins contained blood, and these were considered the main blood vessels, an error undoubtedly based upon the findings in the cadaver. His erroneous doctrines were accepted for several centuries. Erasistratus and Herophilus dissected the heart, the former naming the valves and chordae tendiniae. Both thought there was communication between the arteries and veins, that the arteries were the active elements and the veins the passive. It was Galen (131-201 A.D.) who disposed of the old error that the arteries contained air. He believed that the arteries arose from the heart and the veins from the liver; that diastole was the important active movement of the heart, and that the blood moved in both arteries and veins in the nature of an ebb and flow rather than in a continuous circulation. He recognized the importance of the muscular element in the heart and vessels, and drew the conclusion that since the heart would beat outside the body, the impulse for its contraction must originate within the organ itself. He was the first to describe aneurism of the aorta. In the period of scientific investigation the authors group Aegidius Carboliensis, the student of the pulse; Mondino de Luzzi, who described the heart valves with great accuracy; Leonardo da Vinci, who believed that systole was the important phase of the cardiac cycle; Sylvius, who first described the foramen ovale; Winter, who studied the muscular functions and the valves; Vesalius, who destroyed the Galenic view of pores communicating between the two ventricles, although retaining his views of separate arterial and venous circulations; Servetus, who described the pulmonary circulation as separate from the system; Realdo Columbus, who is thought to have been the discoverer of the pulmonary circulation; Brisset, the reformer of venesection; Fabricius, the teacher of Harvey; Anohea Cesalpino, who first used the word circulation, and discovered the direction of the venous blood; and Harvey, who completed the discovery of the circulation. Following Harvey came Malpighi, the discoverer of the capillaries and the red blood cells; Brelli, who attempted to calculate the contraction power per unit volume of the cardiac chambers; Stensen, who studied the muscular contraction of the heart; Mayow, who showed that the object of respiration was the exchange of gases between the air and blood; Glisson, who studied the muscular contractions; Lancisi, who attempted a classification of cardiac disease and made observations on aneurism and cardiac syphilis; Morgagni, who is said to have recorded the first case of heart block; Lomer, with his experiments of transfusion and infusion; Keill, who made extensive studies on the force of the heart beat; Hales, the first to estimate blood

pressure; von Haller, who proposed the myogenic theory of the heart beat; and Senac, who published a work on the heart, its action and diseases. In the period of scientific application the authors place Auenbrugger, Corvisart, Withering, Stokes, Corrigan, Bright, Hodgson, Laennec, Bouilland, Poiseuille, Ludvig, Louis, Hope, Potain, Traube, Morrey, Gaskell, Engelmann, Kent and His, mentioning the especial contribution of each to cardiology. A final section is then devoted to "three recent cardiologists',' Theodor Schott, J. M. Groedel and Sir James Mackenzie, with a description of their contributions to technical cardiology. The monograph is a most convenient resume of the high spots in the development of our knowledge of the anatomy, physiology and pathology of the heart, and of the practical application of this knowledge in the treatment of cardiac disease.

Cancer Control. Lake Mohawk Conference, 1926. Report of an International Symposium Held under the Auspices of the American Society for the Control of Cancer, Lake Mohawk, New York, September 20-24, 1926. 336 pages. The Surgical Publishing Company, 1927.

This is an elaborate account of the Lake Mohawk Symposium, the expenses of publication being borne by the Harry M. Lasker Memorial Fund. It contains the purpose and plan of the meeting by George A. Soper, the greeting to the foreign guests by William H. Welch, and the response for the foreign guests by Sir Bland-Sutton. The reports of the executive sessions contain addresses by Bland-Sutton, W. Sampson Handley, Hartmann, Besard, Marie, DuBois, Reverdin, Maisin, Tribiger, Bastionelli, Blumenthal, Balfour, Greenough, Regaud, Bierich, Soper, Bloodgood, Ewing, Roussy, Murray, Wood, Leitch, deVries, Deelman, Dublin, Semken, Saltztein, and Lillienthal. While these addresses contain much of interest about Cancer Prevention and Control Propaganda in the various countries represented by the speakers, very little of scientific value was presented. It was a meeting of propagandists, rather than one of scientific students of cancer, and, therefore, should be judged from this standpoint alone. In this respect they give valuable information as to how much has been accomplished in Europe and this country towards the prevention and control of cancer. The matters discussed were largely those of morbidity and mortality statistics. Radiological treatment also received attention from Greenough and Regaud. Ewing's article on the prevention of cancer is sane and sensible, and is by far the best and most practical address given at this conference. The lack of agreement on such vital points is very well shown, however, by a comparison of his paper with that of Balfour of Rochester, Minnesota. In his paper on "Cancer of the Stomach" he states that "the removal of gastric ulcers will contribute largely to the control of cancer of the stomach and should be included in the educational campaign of the Society." Ewing in his paper says: "Assigning 5-10 per cent of gastric cancers to gastric ulcers, the excision of ulcers may be given credit for the prevention of a small proportion of cancers, but at the cost of considerable mortality." Roussy's review of the "New Theories of the Origin of Cancer" will be of interest to medical readers and students. deVries analyzes mortality returns and concludes that "mortality returns give too favorable an impression of the prevalence of cancer in general, and probably also of some important forms of cancer (stomach and intestine). The figures for some external cancers may be considered as fairly correct. Autopsy and mortality returns together give us a fairly correct idea of the importance of cancer. Therefore, postmortem examinations and specification in mortality returns must be encouraged." Deelman's paper on "Mortality among Different Races" is of interest in showing that race apparently has no relation to cancer incidence. The papers mentioned are the most interesting and practical ones, although the whole volume should be read by all interested in cancer for the light thrown upon the mental attitudes of many of those interested in cancer propaganda. We have already in an editorial called attention to the formal resolutions

adopted at this conference, and their weak-kneed attitude regarding hereditary susceptibility in cancer etiology.

The Beaver: Its Work and Its Ways. By EDWARD R. WARREN, S.B., Collaborator, the Roosevelt Wild Life Forest Experiment Station, New York State College of Forestry, Syracuse, N. Y.; late Director of the Museum, Colorado College. Monographs of the American Society of Mammalogists, No. 2. 177 pages, xiii chapters, 71 line cuts, 73 half tones, Bibliography. Index. The Williams and Wilkins Company, Baltimore, Maryland, 1927. Price in cloth, $3.00.

This book gives in a simple and non-technical language a full account of the life and habits of the most interesting small animal common to the North American continent. It is a book for the general reader as well as for students of science, and will make an especial appeal to those medical men who are interested in out-of-doors and in wild life. The first chapter gives a complete description of the animal and its different varieties, and this is followed by one on its ancestry and a description of the giant beaver. Other chapters tell in a most interesting manner the story of many observations on the intelligence of the beaver, the construction of beaver dams and lodges, canals, trails and landing places. Beaver meadows are described, the animal's food and methods of tree-cutting are discussed in detail. Other chapters are concerned with the general habits of the animal, its breeding and family life, its manner of swimming and walking, its voice, its diseases, enemies and parasites. All of these chapters are illustrated freely with most interesting photographs. Its relation to fish and to bird life are discussed. A chapter is devoted to beaver fur, meat and beaver farming. What a beaver does not do is also told. This is a good book for anyone's nature library.

College News Notes

The protracted illness of Dr. John Lichty, Superintendent of the Clifton Springs Sanatorium and Clinic of Clifton Springs, New York, has made it impossible for him to participate during the past few months in the work of The College. Dr. Lichty as Regent and Chairman of the Committee on Credentials has, for a long time, rendered great service to The College. His full and early recovery is sincerely hoped for by all members of The College.

B. T. McGhie, M.D.C.M., who for the past seven and a half years has held the position of Medical Superintendent of Westminster Psychopathic Hospital, a Federal Institution situated at London, Ontario, has been appointed to the position of Medical Superintendent to the Ontario Hospital, Orillia, Ontario, and will, after November 1st, have charge of the care of mental defectives in the Province at that institution.

Dr. Edgar M. Green (Fellow, February 21, 1924), of Easton, Pa., has been appointed a member of the Board of Medical Education and Licensure, to fill the vacancy caused by the resignation of Dr. Walter Estell Lee, of Philadelphia, Pa.

Dr. James E. Talley (Fellow, February 20, 1924) was recently elected Vice President of the Philadelphia Heart Association.

Dr. Hyman I. Goldstein (Associate, January 1, 1921) has been appointed Chief of the Medical Diagnostic Clinic of the Mt. Sinai Hospital of Philadelphia.

Obituaries

Dr. Frank Tyler Stephenson, Detroit, Michigan—May 14, 1927. Appendicitis. Elected a Fellow of The College July 24, 1919.

Dr. Clyde Fenworth Karshner, Grand Rapids, Michigan—June 10, 1927. Splenic Anemia. Elected a Fellow of The College December 27, 1919.